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(57) Abstract

A novel protein tyrosine kinase, JAK3, and a polynucleotide sequence encoding JAK3 polypeptide are disclosed herein. JAK3 is a new member of the JAK family of protein tyrosine kinases which are important in regulation of cellular proliferation and differentiation. Also disclosed are therapeutic methods utilizing JAK3 polypeptide and polynucleotide sequences.

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NOVEL PROTEIN TYROSINE KINASE, JAK3

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BACKGROUND OF THE INVENTION

1. *Field of the Invention*

The present invention relates generally to a protein tyrosine kinases and specifically to JAK3, a novel protein tyrosine kinase of the JAK family.

2. *Description of Related Art*

Proliferation and differentiation of hematopoietic cells is dependent upon the binding of hematopoietic growth factors and cytokines to their respective cell surface receptors (Cross, *et al.*, *Cell*, 64:271, 1991; Ogawa, M., *Blood*, 81:2844, 1993; Heimfeld, S., *et al.*, *Proc. Natl. Acad. Sci. USA*, 88:9902, 1991). Some of these receptors transduce the signal at the cell surface to the cytoplasm through the activation of a tyrosine kinase domain in the cytoplasmic portion of the receptor (*eg.*, CSF1, c-kit, STK-1/FLT3/FLK2-) (Boyle, W.J., *Current Opinion in Oncology*, 4:156, 1992, Chiba, T., *et al.*, *Nature*, 362:646, 1993, Schlessinger, J., *et al.*, *Neuron*, 9:383, 1992, Ullrich, A. and Schlessinger, J., *Cell*, 61:203, 1990). Another group of hematopoietic receptors lack intrinsic kinase catalytic domains (*e.g.*, IL-3, GM-CSF, G-CSF, and EPO receptors) (Miyajima, A., *et al.*, *Blood*, 82:1960, 1993, Fukunaga, R., *et al.*, *EMBO*, 10:2855, 1991, Wojchowski, D.M., *et al.*, *Stem Cells*, 11:381, 1993), however, upon binding of their ligands, these receptors activate protein tyrosine phosphorylation of second messengers and the subsequent signal pathways to the cell's nucleus (Kishimoto, T. *et al.*, *Science*, 258:593, 1992, Stahl, N., *et al.*, *Cell*, 74:587, 1993).

Tyrosine kinases often play pivotal roles in the proliferation and differentiation of many cell types. Many growth factor receptors contain a tyrosine kinase domain as

part of their cytoplasmic tail such that binding by ligand directly activates their tyrosine kinase activity. However, many other receptors do not contain a tyrosine kinase domain in their cytoplasmic tail. Addition of ligand to many cell types expressing these receptors still results in increased levels of phosphotyrosine. The JAK family, a series of related intracellular tyrosine kinases, has recently been shown to link these receptors and other members of the signal transduction pathway.

The JAK family members contain the highly conserved catalytic domain found in other tyrosine kinases (Firmbach-Kraft, I., *et al.*, *Oncogene*, 5:1329, 1990, Hanks, S.K., *et al.*, *Methods in Enzymology*, 200: 38, 1991, Hunter, T., *Methods in Enzymology*, 200:3, 1991, Wilks, A.F., *Proc. Natl. Acad. Sci. USA*, 86:1603, 1989). One feature that distinguishes the JAK family from other tyrosine kinases is that each member also contains a second kinase-like domain of unknown function (Harpur, A.G., *et al.*, *Oncogene*, 7:1347, 1992). In addition, the JAK family members do not contain SH2 or SH3 domains, signal peptide sequences, or transmembrane domains, and are localized in the cytoplasm (Wilks, A.F., *et al.*, *Molecular and Cellular Biology*, 11:2057, 1991).

Three members of the JAK family, JAK1, JAK2, an TYK-2, have been functionally described. The first two members were isolated by a PCR approach utilizing degenerate oligonucleotide primers and TYK-2 was isolated by screening with a tyrosine kinase probe at reduced stringency (Silvennoinen, O. *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:8429, 1993). To date, the JAK family members have been shown to be involved with the receptors for numerous cytokines and growth factors, including IFN $\alpha\beta$ and γ, IL-3, GM-CSF, EPO, GH, CNTF, LIF, OSM, IL-6, and PRL (Argetsinger, L.S., *et al.*, *Cell*, 74:237, 1993, Lüttichen, C., *et al.*, *Science*, 263:89, 1994, Müller, M., *et al.*, *Nature*, 366:129, 1993, Stahl, N., *et al.*, *Science*, 263:92, 1994, Velazquez, L., *et al.*, *Cell*, 70:313, 1992, Watling, D., *et al.*, *Nature*, 366:166, 1993, Witthuhn, B.A., *et al.*, *Cell*, 74:227, 1993, Rui, H., *et al.*, *The Journal of Biological Chemistry*, 269:5364, 1994). In most cases, the JAK family members seem to associate with the proximal membrane portion of the cytoplasmic domain of the receptor (*e.g.*, gp130, LIFRβ, EPO) as a constitutive complex (Narazaki, M., *et al.*, *Proc. Natl. Acad. Sci. USA*, 91:2285, 1994). In other cases, the association is not

evident until ligand binding takes place (*e.g.*, GH receptor). In either case, ligand binding results in increased JAK kinase activity.

The first evidence for the functional role of JAK family members was provided when it was shown that TYK-2 could rescue IFNα/β responsiveness in a cell line that had become unresponsive. In a similar fashion, JAK1 and JAK2 have been shown to function in the signalling of interferon pathways, as well. In each case, two different JAKS have been found to act with each type of IFN receptor; JAK2 and TYK-2 are involved exclusively with IFN γ and IFN α/β, respectively, whereas JAK1 is involved with both receptors. Stimulation of the IFNα/β receptors by the binding of their respective ligands results in the phosphorylation of p91 (STAT1) and p113 (STAT2), which are subunits of the ISGF3 transcription complex that binds the interferon-stimulated response element (ISRE). In the case of IFNγ, p91 alone is phosphorylated, which then binds gamma-activated sequences (GAS) of IFNγ activated genes (Shual, K., *et al.*, *Nature*, 366:580, 1993, Ihle, J.N., *et al.*, *Trends in Biological Science*, 19:222, 1994). Because each of these receptors associate with JAK1 it has been suggested that JAK1 may directly phosphorylate p91 (Loh, J.E., *et al.*, *Molecular and Cellular Biology*, 14:2170, 1994). It has been recently reported that IL-6 (via gp130), which associates with JAK1 and TYK-2, also triggers the activation of p91 (STAT1) (Yuan, J., *et al.*, *Molecular and Cellular Biology*, 14:1657, 1994). The EPO, and IL-3 receptors are also believed to similarly activate STAT family members. As all of the hematopoietic receptors seem to utilize certain common proteins in their signal transduction pathways, some of the specificity of the pathways may reside in the cell specific expression of STAT family members and their activation by JAK family members (Metcalf, D., *Blood*, 82:3515, 1993, Darnell, J.E., *et al.*, *Science*, 264:1415, 1994).

Additional pairs of JAK family members have been found to associate with other receptors (*e.g.*, CNTF, LIF, IL-6) and both become tyrosine phosphorylated upon the stimulation of these receptors (Silvennoinen, O., *et al.*, *Nature*, 366:583, 1993). It is possible that reciprocal tyrosine phosphorylation between two JAKs is required as

phosphorylation of both associating JAKs is necessary for signal transduction to occur. Thus, JAK family members may act in pairs, possibly as heterodimers.

Recently a Drosophila JAK family member, *hop*, was shown to be required maternally for normal embryonic development (Binari, *et al.*, *Genes & Dev.*, 8:300, 1994). Mutants in *hop* showed defects in the expression of several paired-rule and segment polarity genes, implicating it in the control of transcription of these genes, a role that could be analogous to the defect in TYK-2, JAK1, or JAK2 in several cell lines that lost IFN responsiveness.

The present invention provides a new member of the JAK protein tyrosine kinase family. The structural homology between the JAK3 of this invention and the other members of JAK family, indicates that JAK3 is a new member of this family of non-receptor tyrosine kinases. In analogy to the other JAK family members, JAK3 is likely involved in the signal transduction pathway of already characterized receptors which lack intrinsic activity. Because of its strong expression in the fraction enriched for CD34+ normal human bone marrow, JAK3 is likely to be important in stem/progenitor cell growth, and/or survival, and/or differentiation, by transducing the signals of receptors which modulate these processes. In addition, JAK3 may also be involved in the signal transduction pathways of any of several already known or as yet unidentified non-tyrosine kinase receptors with which the other JAK members have not been shown to associate (*e.g.* IL-2, IL-4,IL-11).

SUMMARY OF THE INVENTION

The present invention provides a novel protein tyrosine kinase JAK3, a polynucleotide sequence which encodes JAK3 and antibodies which are immunoreactive with the protein. The amino acid sequence of JAK3 indicates that it is a new member of the JAK family of non-receptor tyrosine kinases. JAK3 is highly expressed in the CD34+/lin- fraction in normal human bone marrow which is highly enriched in hematopoietic stem/progenitor cells. Therefore, by analogy to other JAK family members, it is likely that JAK3 plays a role in the growth factor modulated differentiation/proliferation/survival of the stem/progenitor cells.

JAK3 is expressed in mammalian tissues, and particularly human tissue. For example, JAK3 is expressed in human hematopoietic tissues, (*e.g.*, bone marrow), and non-hematopoietic human tissues, such as liver, lung, kidney, spleen and intestine. In particular, JAK-3 is most highly expressed in the stem/progenitor cell enriched fraction of normal human bone marrow. JAK-3 is further expressed in a wide range of leukemic derived cell lines including AMLs (KG1, TF-1, HEL), B lineage ALLs (PB697, Nalm-16, and Nalm-6), and T-ALLs (Molt-16, and Molt-3).

JAK3 is localized to chromosome 19, band p12-13.1, where the another member of the JAK family, TYK-2 is co-localized. Several other genes containing tyrosine kinase domains are tandemly linked and may have evolved by cis duplications. Examples include the genes for the receptors of c-fms (CSF-1 receptor) and PDGFR β on chromosome 5 bands q31-q33, c-kit and PDGFR α on chromosome 4 bands q11-q13, as well as FLT1 and STK-1/FLT3/FLK2 on chromosome 13 band q12.

In another embodiment, the invention provides a method for ameliorating a cell proliferative disorder associated with JAK-3. In another embodiment, the invention provides a method for stimulating stem/progenitor cell proliferation/survival and differentiation *in vitro*.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows nucleotide (cDNA) and predicted amino acid sequence of JAK3, (SEQ ID NO:1 and NO:2, respectively. The predicted amino acids are numbered on the left of each column with the nucleotides of the largest open reading frame numbered on the right, starting with the initiating methionine of JAK3. The conserved tyrosine kinase motifs GXGXXG and DFG are shown boxed. The highly conserved peptide regions chosen for the design of the degenerate oligo nucleotides used for the initial PCR [VHRDLA & DVWSFG] are shown in ovals. Also shown are 167 bases of the 5' untranslated region and 394 bases of the 3' untranslated region. Potential polyadenylation signals are underlined.

FIGURE 2 shows an amino acid comparison between JAK3 and other JAK family members. The numbering system begins with the initiating methionine of the JAK family members. The numbering system does not take into account the insertion of gaps and, therefore, should be only regarded as a relative measure of location. The consensus sequence (CONS) is derived if three out of four JAK family members have the identical amino acid in that position. The conserved kinase domain of all tyrosine kinases, JAK homology domain 1 (JH1), and the putative second kinase domain, JAK homology domain 2 (JH2) are designated with arrows. With the exception of JAK2, (murine), all sequences are human.

FIGURE 3 shows an amino acid comparison between human JAK3 and rat JAK3. The amino acid residues of each member are numbered beginning with the initiating methionine. The consensus sequence (CONS) of the two JAK family members are listed below the compared sequences when identical. Pluses (+) denote conservative amino acid substitutions.

FIGURE 4a shows an RNAse protection analysis of JAK3 expression in human leukemia derived cell lines and normal bone marrow. On the left side the undigested full-length JAK3 and actin probes are denoted. The RNA sources are labeled above each lane. To show the specificity of the protected bands, reactions with no RNA and with tRNA (tRNA) were also conducted. The position of the protected JAK3 and actin species are denoted on the right side.

FIGURE 4b shows a northern blot analysis of JAK3 expression in human leukemia derived cell lines. (Upper half) A Northern blot of poly A+ RNA from the leukemia-derived cell lines noted above each lane was hybridized with a randomly primed ^{32}P α-dCTP labeled probe corresponding to a 1.8 kb fragment of JAK3. The relative mobilities of the 28S ribosomal RNA and RNA markers are denoted on the right. The JAK3 band is indicated by an arrow. (Lower half) The blot was stripped and reprobed with actin.

FIGURE 4c shows a northern blot analysis of JAK3 expression in non-hematopoietic tissues. A multiple tissue Northern blot (Clonetech, Palo Alto, CA) containing 2 ug of poly A+ RNA from human heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas was hybridized with the same probe as in Figure 4b. The relative mobilities of the RNA markers are denoted on the left. The JAK3 band is indicated by an arrow.

FIGURE 5a shows an RNAse protection analysis of JAK3 expression in normal bone marrow fractions. On the left side the undigested, full-length, JAK3 and actin probes are denoted. The RNA sources are labeled above each lane. To show the specificity of the protected bands, reactions with no RNA (None) and with tRNA (tRNA) were also conducted. The protected JAK3 and actin species are denoted on the right side. The unlabelled band that migrates between the JAK3 and actin bands is present in all lanes, including the no RNA and tRNA lanes, and is a result of incomplete digestion of the probe.

FIGURE 5b shows a phosphorimage analysis of bone marrow fractions. Following exposure to film, the gel shown in Figure 5a was exposed to a phosphorimage screen (Molecular Dynamics, Sunnyvale, CA). Bands were quantified using the ImageQuantify program and normalized relative to the actin signals.

FIGURE 6a shows fluorescence *in situ* hybridization (FISH) used to identify the localization of JAK3. A plasmid containing approximately 80kb of the JAK3 genomic DNA was labelled with biotin-14 dATP and hybridized to chromosome spreads made from normal human male lymphocytes cultured with BrdU. Analysis of 36 metaphase cells showed 20 cells (56%) had at least one pair of signals (involving both chromatids of a single chromosome), an example of which is shown. Paired signals are indicated by arrows.

FIGURE 6b shows G-banding of chromosome spreads. The same metaphase spread shown in FIGURE 6a was G-banded by fluorescence plus Giemsa (FPG) after hybridization, photographed and aligned with the color FISH slides. The position of the paired FISH signals on the G-banded chromosomes are indicated by arrows.

FIGURE 6c shows an ideogram of human chromosome 19, revealing localization of JAK3 to 19p12-13.1. Each dot represents a paired signal seen on metaphase chromosomes. Signals clearly located on a single band are diagrammed to the right of the ideogram; those which could not be sublocalized to a single band are assigned to regions diagrammed to the left (brackets).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel protein tyrosine kinase, JAK3, and a polynucleotide sequence encoding JAK3 polypeptide. The amino acid sequence of JAK3 indicates that it is a new member of the JAK family of non-receptor tyrosine kinases. In normal human bone marrow, JAK3 is highly expressed in the CD34+/lin- fraction which is enriched in hematopoietic stem/progenitor cells. As JAK kinases have been shown to be involved in the signal transduction pathways of various

hematopoietic growth factors, it is likely that JAK3 plays a role in the growth factor modulated differentiation/proliferation/survival of hematopoietic stem/progenitor cells.

In a first embodiment, the invention provides a substantially pure JAK3 polypeptide consisting essentially of the amino acid sequence of SEQ ID NO:2. The full-length JAK3 polypeptide sequence has 1082 amino acids with a molecular weight of approximately 121 kD. JAK3 has 48% identity and 67% similarity with JAK2 (murine), 41% identity and 61% similarity with JAK1 (human), and 40% identity and 60% similarity with TYK-2 (human). Comparison of human JAK3 with the rat JAK3 shows 77% identity and 84% similarity (Takahashi, T. and Shirasawa, T., *FEBS Letters*, 342:124, 1994).

The term "substantially pure" or "isolated" as used herein, refers to JAK3 polypeptide which is substantially free of other proteins, lipids, carbohydrates, nucleic acids, or other materials with which it is naturally associated. One skilled in the art can purify JAK3 using standard techniques for protein purification. The substantially pure polypeptide will yield a single major band on a non-reducing polyacrylamide gel. The purity of the JAK3 polypeptide can also be determined by amino-terminal amino acid sequence analysis.

The invention includes a functional polypeptide, JAK3, and functional fragments thereof. As used herein, the term "functional polypeptide" refers to a polypeptide which possesses a biological function or activity which is identified through a defined functional assay and which is associated with a particular biologic, morphologic, or phenotypic alteration in the cell. Functional fragments of the JAK3 polypeptide, includes fragments of JAK3 as long as the activity, *e.g.*, protein tyrosine kinase activity, of JAK3 remains. Smaller peptides containing the biological activity of JAK3 are included in the invention. The biological function, for example, can vary from a polypeptide fragment as small as an epitope to which an antibody molecule can bind to a large polypeptide which is capable of participating in the characteristic induction or programming of phenotypic changes within a cell. An enzymatically

functional JAK3 polypeptide or fragment thereof possesses JAK3 tyrosine kinase activity. A "functional polynucleotide" denotes a polynucleotide which encodes a functional polypeptide as described herein.

Minor modifications of the JAK3 primary amino acid sequence may result in proteins which have substantially equivalent activity as compared to the JAK3 polypeptide described herein. Such modifications may be deliberate, as by site-directed mutagenesis, or may be spontaneous. All of the polypeptides produced by these modifications are included herein as long as the tyrosine kinase activity of JAK3 is present. Further, deletion of one or more amino acids can also result in a modification of the structure of the resultant molecule without significantly altering its kinase activity. This can lead to the development of a smaller active molecule which may have broader utility. For example, it is possible to remove amino or carboxyl terminal amino acids which may not be required for JAK3 kinase activity.

The JAK3 polypeptide of the invention also includes conservative variations of the polypeptide sequence. The term "conservative variation" as used herein denotes the replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include the substitution of one hydrophobic residue such as isoleucine, valine, leucine or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like. The term "conservative variation" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide.

The invention also provides an isolated polynucleotide sequence consisting essentially of a polynucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:2. As used herein, "polynucleotide" refers to a polymer of deoxyribonucleotides or ribonucleotides, in the form of a separate fragment or a larger construct. The term "isolated" as used herein includes polynucleotides substantially free of other nucleic acids, proteins, lipids, carbohydrates or other materials with

which it is naturally associated. Polynucleotide sequences of the invention include DNA, cDNA and RNA sequences which encode JAK3. It is understood that all polynucleotides encoding all or a portion of JAK3 are also included herein, as long as they encode a polypeptide with JAK3 kinase activity. Such polynucleotides include naturally occurring, synthetic, and intentionally manipulated polynucleotides. For example, JAK3 polynucleotide may be subjected to site-directed mutagenesis. The polynucleotide sequence for JAK3 also includes antisense sequences. The polynucleotides of the invention include sequences that are degenerate as a result of the genetic code. There are 20 natural amino acids, most of which are specified by more than one codon. Therefore, all degenerate nucleotide sequences are included in the invention as long as the amino acid sequence of JAK3 polypeptide encoded by the nucleotide sequence is functionally unchanged. In addition, the invention also includes a polynucleotide consisting essentially of a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO:2 and having at least one epitope for an antibody immunoreactive with JAK3 polypeptide.

Specifically disclosed herein is a cDNA sequence which encodes JAK3 which comprising a 3,807 base pair (bp) predicted coding region for JAK3, 167 base pairs of 5' untranslated and 394 base pairs of 3' untranslated sequence (SEQ. ID NO:1). The cDNA includes an open reading frame of 3,246 base pairs encoding a protein of about 1082 amino acids, having a molecular weight of about 121 kD. The putative initiating methionine shows the strongest homology with the Kozak consensus sequence (Kozak, M., *Nucleic Acids Research*, 15:8125, 1987). At the 3' end, an in frame stop codon defines the C-terminus of the JAK3 protein at position 3242.

The polynucleotide encoding JAK3 includes the nucleotide sequence in FIGURE 1 (SEQ ID NO:1), as well as nucleic acid sequences complementary to that sequence. A complementary sequence may include an antisense nucleotide. When the sequence is RNA, the deoxynucleotides A, G, C, and T of FIGURE 1 are replaced by ribonucleotides A, G, C, and U, respectively. Also included in the invention are fragments of the above-described nucleic acid sequences that are at least 15 bases in

length, which is sufficient to permit the fragment to selectively hybridize to DNA that encodes the protein of FIGURE 1 (SEQ ID NO: 2) under physiological conditions.

DNA sequences of the invention can be obtained by several methods. For example, the DNA can be isolated using hybridization techniques which are well known in the art. These include, but are not limited to: 1) hybridization of genomic or cDNA libraries with probes to detect homologous nucleotide sequences; 2) antibody screening of expression libraries to detect cloned DNA fragments with shared structural features; and 3) PCR amplification of a desired nucleotide sequence using oligonucleotide primers.

Preferably the JAK3 polynucleotide of the invention is derived from a mammalian organism, and most preferably from human. Screening procedures which rely on nucleic acid hybridization make it possible to isolate any gene sequence from any organism, provided the appropriate probe is available. Oligonucleotide probes, which correspond to a part of the sequence encoding the protein in question, can be synthesized chemically. This requires that short, oligopeptide stretches of amino acid sequence must be known. The DNA sequence encoding the protein can be deduced from the genetic code, however, the degeneracy of the code must be taken into account. It is possible to perform a mixed addition reaction when the sequence is degenerate. This includes a heterogeneous mixture of denatured double-stranded DNA. For such screening, hybridization is preferably performed on either single-stranded DNA or denatured double-stranded DNA. Hybridization is particularly useful in the detection of cDNA clones derived from sources where an extremely low amount of mRNA sequences relating to the polypeptide of interest are present. In other words, by using stringent hybridization conditions directed to avoid non-specific binding, it is possible, for example, to allow the autoradiographic visualization of a specific cDNA clone by the hybridization of the target DNA to that single probe in the mixture which is its complete complement (Wallace, *et al., Nucl. Acid Res.*, 9:879, 1981).

The development of specific DNA sequences encoding JAK3 can also be obtained by: 1) isolation of double-stranded DNA sequences from the genomic DNA; 2) chemical manufacture of a DNA sequence to provide the necessary codons for the polypeptide of interest; and 3) *in vitro* synthesis of a double-stranded DNA sequence by reverse transcription of mRNA isolated from a eukaryotic donor cell. In the latter case, a double-stranded DNA complement of mRNA is eventually formed which is generally referred to as cDNA.

Of the three above-noted methods for developing specific DNA sequences for use in recombinant procedures, the isolation of genomic DNA isolates is the least common. This is especially true when it is desirable to obtain the microbial expression of mammalian polypeptides due to the presence of introns.

The synthesis of DNA sequences is frequently the method of choice when the entire sequence of amino acid residues of the desired polypeptide product is known. When the entire sequence of amino acid residues of the desired polypeptide is not known, the direct synthesis of DNA sequences is not possible and the method of choice is the synthesis of cDNA sequences. Among the standard procedures for isolating cDNA sequences of interest is the formation of plasmid- or phage-carrying cDNA libraries which are derived from reverse transcription of mRNA which is abundant in donor cells that have a high level of genetic expression. When used in combination with polymerase chain reaction technology, even rare expression products can be cloned. In those cases where significant portions of the amino acid sequence of the polypeptide are known, the production of labeled single or double-stranded DNA or RNA probe sequences duplicating a sequence putatively present in the target cDNA may be employed in DNA/DNA hybridization procedures which are carried out on cloned copies of the cDNA which have been denatured into a single-stranded form (Jay, *et al.*, *Nucl. Acid Res.*, 11:2325, 1983).

A preferred method for obtaining genomic DNA for example is Polymerase Chain Reaction (PCR), which relies on an *in vitro* method of nucleic acid synthesis by which a particular segment of DNA is specifically replicated. Two oligonucleotide primers

that flank the DNA fragment to be amplified are utilized in repeated cycles of heat denaturation of the DNA, annealing of the primers to their complementary sequences, and extension of the annealed primers with DNA polymerase. These primers hybridize to opposite strands of the target sequence and are oriented so that DNA synthesis by the polymerase proceeds across the region between the primers. Since the extension products themselves are also complementary to and capable of binding primers, successive cycles of amplification essentially double the amount of the target DNA synthesized in the previous cycle. The result is an exponential accumulation of the specific target fragment, approximately 2^n, where n is the number of cycles of amplification performed (see PCR Protocols, Eds. Innis, *et al.*, Academic Press, Inc., 1990, incorporated herein by reference).
A cDNA expression library, such as lambda gt11, can be screened indirectly for JAK3 peptides having at least one epitope, using antibodies specific for JAK3. Such antibodies can be either polyclonally or monoclonally derived and used to detect expression product indicative of the presence of JAK3 cDNA.

The polynucleotide sequence for JAK3 also includes sequences complementary to the polynucleotide encoding JAK3 (antisense sequences). Antisense nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule (Weintraub, *Scientific American*, 262:40, 1990). The invention embraces all antisense polynucleotides capable of inhibiting production of JAK3 polypeptide. In the cell, the antisense nucleic acids hybridize to the corresponding mRNA, forming a double-stranded molecule. The antisense nucleic acids may interfere with the translation of the mRNA since the cell will not translate a mRNA that is double-stranded, or alternatively, the double-stranded mRNA is degraded. Antisense oligomers of about 15 nucleotides are preferred, since they are easily synthesized, small enough to enter the cell, and are less likely to cause problems than larger molecules when introduced into the target JAK3-producing cell. The use of antisense methods to inhibit the translation of genes is well known in the art (Marcus-Sakura, *Anal. Biochem.*, 172:289, 1988).

In addition, ribozyme nucleotide sequences for JAK3 are included in the invention. Ribozymes are RNA molecules possessing the ability to specifically cleave other single-stranded RNA in a manner analogous to DNA restriction endonucleases. Through the modification of nucleotide sequences which encode these RNAs, it is possible to engineer molecules that recognize specific nucleotide sequences in an RNA molecule and cleave it (Cech, *J. Amer. Med. Assn.*, 260:3030, 1988). A major advantage of this approach is that, because they are sequence-specific, only mRNAs with particular sequences are inactivated.

There are two basic types of ribozymes namely, *tetrahymena*-type (Hasselhoff, *Nature*, 334:585, 1988) and "hammerhead"-type. *Tetrahymena*-type ribozymes recognize sequences which are four bases in length, while "hammerhead"-type ribozymes recognize base sequences 11-18 bases in length. The longer the recognition sequence, the greater the likelihood that sequence will occur exclusively in the target mRNA species. Consequently, hammerhead-type ribozymes are preferable to *tetrahymena*-type ribozymes for inactivating a specific mRNA species and 18-based recognition sequences are preferable to shorter recognition sequences.

DNA sequences encoding JAK3 can be expressed *in vitro* by DNA transfer into a suitable host cell. "Host cells" are cells in which a vector can be propagated and its DNA expressed. The term also includes any progeny of the subject host cell. It is understood that all progeny may not be identical to the parental cell since there may be mutations that occur during replication. However, such progeny are included when the term "host cell" is used. Methods of stable transfer, meaning that the foreign DNA is continuously maintained in the host, are known in the art.

In the present invention, the JAK3 polynucleotide sequences may be inserted into a recombinant expression vector. The term "recombinant expression vector" refers to a plasmid, virus or other vehicle known in the art that has been manipulated by insertion or incorporation of the JAK3 genetic sequences. Such expression vectors contain a promoter sequence which facilitates the efficient transcription of the inserted genetic sequence of the host. The expression vector typically contains an origin of

replication, a promoter, as well as specific genes which allow phenotypic selection of the transformed cells. Vectors suitable for use in the present invention include, but are not limited to the T7-based expression vector for expression in bacteria (Rosenberg, *et al.*, *Gene*, 56:125, 1987), the pMSXND expression vector for expression in mammalian cells (Lee and Nathans, *J. Biol. Chem.*, 263:3521, 1988) and baculovirus-derived vectors for expression in insect cells. The DNA segment can be present in the vector operably linked to regulatory elements, for example, a promoter (e.g., T7, metallothionein I, or polyhedrin promoters).

Polynucleotide sequences encoding JAK3 can be expressed in either prokaryotes or eukaryotes. Hosts can include microbial, yeast, insect and mammalian organisms. Methods of expressing DNA sequences having eukaryotic or viral sequences in prokaryotes are well known in the art. Biologically functional viral and plasmid DNA vectors capable of expression and replication in a host are known in the art. Such vectors are used to incorporate DNA sequences of the invention.

Methods which are well known to those skilled in the art can be used to construct expression vectors containing the JAK3 coding sequence and appropriate transcriptional/translational control signals. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* recombination/genetic techniques. See, for example, the techniques described in Maniatis, *et al.*, 1989 Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y.

A variety of host-expression vector systems may be utilized to express the JAK3 coding sequence. These include but are not limited to microorganisms such as bacteria transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing the JAK3 coding sequence; yeast transformed with recombinant yeast expression vectors containing the JAK3 coding sequence; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing the JAK3 coding sequence; insect cell systems infected with recombinant virus expression

vectors (*e.g.*, baculovirus) containing the JAK3 coding sequence; or animal cell systems infected with recombinant virus expression vectors (*e.g.*, retroviruses, adenovirus, vaccinia virus) containing the JAK3 coding sequence, or transformed animal cell systems engineered for stable expression. Since JAK3 has not been confirmed to contain carbohydrates, both bacterial expression systems as well as those that provide for translational and post-translational modifications may be used; *e.g.*, mammalian, insect, yeast or plant expression systems.

Depending on the host/vector system utilized, any of a number of suitable transcription and translation elements, including constitutive and inducible promoters, transcription enhancer elements, transcription terminators, etc. may be used in the expression vector (see *e.g.*, Bitter, *et al.*, 1987, Methods in Enzymology, 153:516-544). For example, when cloning in bacterial systems, inducible promoters such as pL of bacteriophage γ, plac, ptrp, ptac (ptrp-lac hybrid promoter) and the like may be used. When cloning in mammalian cell systems, promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the retrovirus long terminal repeat; the adenovirus late promoter; the vaccinia virus 7.5K promoter) may be used. Promoters produced by recombinant DNA or synthetic techniques may also be used to provide for transcription of the inserted JAK3 coding sequence.

In bacterial systems a number of expression vectors may be advantageously selected depending upon the use intended for the expressed. For example, when large quantities of JAK3 are to be produced, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Those which are engineered to contain a cleavage site to aid in recovering are preferred. Such vectors include but are not limited to the *E. coli* expression vector pUR278 (Ruther, *et al.*, *EMBO J.*, 2:1791, 1983), in which the JAK3 coding sequence may be ligated into the vector in frame with the lac Z coding region so that a hybrid -lac Z protein is produced; pIN vectors (Inouye and Inouye, *Nucleic Acids Res.*, 13:3101, 1985; Van Heeke and Schuster, *J. Biol. Chem.* 264:5503, 1989) and the like.

In yeast, a number of vectors containing constitutive or inducible promoters may be used. For a review see, Current Protocols in Molecular Biology, Vol. 2, 1988, Ed. Ausubel, *et al.*, Greene Publish. Assoc. & Wiley Interscience, Ch. 13; Grant, *et al.*, 1987, Expression and Secretion Vectors for Yeast, in Methods in Enzymology, Eds. Wu and Grossman, 31987, Acad. Press, N.Y., Vol. 153, pp.516-544; Glover, 1986, DNA Cloning, Vol. II, IRL Press, Wash., D.C., Ch. 3; and Bitter, 1987, Heterologous Gene Expression in Yeast, Methods in Enzymology, Eds. Berger and Kimmel, Acad. Press, N.Y., Vol. 152, pp. 673-684; and The Molecular Biology of the Yeast Saccharomyces, 1982, Eds. Strathern, *et al.*, Cold Spring Harbor Press, Vols. I and II. A constitutive yeast promoter such as ADH or LEU2 or an inducible promoter such as GAL may be used (Cloning in Yeast, Ch. 3, R. Rothstein In: DNA Cloning Vol.11, A Practical Approach, Ed. DM Glover, 1986, IRL Press, Wash., D.C.). Alternatively, vectors may be used which promote integration of foreign DNA sequences into the yeast chromosome.

In cases where plant expression vectors are used, the expression of the JAK3 coding sequence may be driven by any of a number of promoters. For example, viral promoters such as the 35S RNA and 19S RNA promoters of CaMV (Brisson, *et al.*, *Nature*, 310:511, 1984), or the coat protein promoter to TMV (Takamatsu, *et al.*, *EMBO J.*, 6:307, 1987) may be used; alternatively, plant promoters such as the small subunit of RUBISCO (Coruzzi, *et al.*, *EMBO J.*, 3:1671-1680, 1984; Broglie, *et al.*, *Science*, 224:838, 1984); or heat shock promoters, *e.g.*, soybean hsp17.5-E or hsp17.3-B (Gurley, *et al.*, *Mol. Cell. Biol.*, 6:559, 1986) may be used. These constructs can be introduced into plant cells using Ti plasmids, Ri plasmids, plant virus vectors, direct DNA transformation, microinjection, electroporation, etc. For reviews of such techniques see, for example, Weissbach and Weissbach, 1988, Methods for Plant Molecular Biology, Academic Press, NY, Section VIII, pp. 421-463; and Grierson and Corey, 1988, Plant Molecular Biology, 2d Ed., Blackie, London, Ch. 7-9.

An alternative expression system which could be used to express is an insect system. In one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda*

cells. The JAK3 coding sequence may be cloned into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of the JAK3 coding sequence will result in inactivation of the polyhedrin gene and production of non-occluded recombinant virus (*i.e.*, virus lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect *Spodoptera frugiperda* cells in which the inserted gene is expressed. (*e.g.*, see Smith, *et al.*, *J. Viol.*, 46:584, 1983; Smith, U.S. Patent No. 4,215,051).

Eukaryotic systems, and preferably mammalian expression systems, allow for proper post-translational modifications of expressed mammalian proteins to occur. Eukaryotic cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, phosphorylation, and advantageously, secretion of the gene product may be used as host cells for the expression of JAK3. Mammalian cell lines may be preferable. Such host cell lines may include but are not limited to CHO, VERO, BHK, HeLa, COS, MDCK, -293, and WI38.

Mammalian cell systems which utilize recombinant viruses or viral elements to direct expression may be engineered. For example, when using adenovirus expression vectors, the JAK3 coding sequence may be ligated to an adenovirus transcription/-translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the protein in infected hosts (*e.g.*, see Logan and Shenk, *Proc. Natl. Acad. Sci. USA*, 81:3655, 1984). Alternatively, the vaccinia virus 7.5K promoter may be used. (*e.g.*, see, Mackett, *et al.*, *Proc. Natl. Acad. Sci. USA*, 79:7415, 1982; Mackett, *et al.*, *J. Virol.*, 49: 857, 1984; Panicali, *et al.*, *Proc. Natl. Acad. Sci. USA*, 79:4927, 1982). Of particular interest are vectors based on bovine papilloma virus which have the ability to replicate as extrachromosomal elements (Sarver, *et al.*, *Mol. Cell. Biol.*, 1:486, 1981). Shortly after entry of this DNA into mouse cells, the plasmid replicates to about 100 to 200 copies per cell. Transcription of the inserted cDNA does not

require integration of the plasmid into the host's chromosome, thereby yielding a high level of expression. These vectors can be used for stable expression by including a selectable marker in the plasmid, such as, for example, the neo gene. Alternatively, the retroviral genome can be modified for use as a vector capable of introducing and directing the expression of the JAK3 gene in host cells (Cone and Mulligan, *Proc. Natl. Acad. Sci. USA*, 81:6349, 1984). High level expression may also be achieved using inducible promoters, including, but not limited to, the metallothionine IIA promoter and heat shock promoters.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with the JAK3 cDNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. For example, following the introduction of foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler, *et al.*, *Cell*, 11: 223, 1977), hypoxanthine-guanine phosphoribosyltransferase (Szybalska and Szybalski, *Proc. Natl. Acad. Sci. USA*, 48:2026, 1962), and adenine phosphoribosyltransferase (Lowy, *et al.*, *Cell*, 22: 817, 1980) genes can be employed in tk$^-$, hgprt$^-$ or aprt$^-$ cells respectively. Also, antimetabolite resistance can be used as the basis of selection for dhfr, which confers resistance to methotrexate (Wigler, *et al.*, *Natl. Acad. Sci. USA*, 77: 3567, 1980; O'Hare, *et al.*, *Proc. Natl. Acad. Sci. USA*, 78: 1527, 1981); gpt, which confers resistance to mycophenolic acid (Mulligan and Berg, *Proc. Natl. Acad. Sci. USA*, 78: 2072, 1981; neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, *et al.*, *J. Mol. Biol.*, 150:1, 1981); and hygro, which confers resistance to hygromycin (Santerre, *et al.*, *Gene*, 30:147, 1984) genes. Recently, additional selectable genes have been described, namely trpB, which allows cells to utilize

indole in place of tryptophan; hisD, which allows cells to utilize histinol in place of histidine (Hartman and Mulligan, *Proc. Natl. Acad. Sci. USA*, 85:8047, 1988); and ODC (ornithine decarboxylase) which confers resistance to the ornithine decarboxylase inhibitor, 2-(difluoromethyl)-DL-ornithine, DFMO (McConlogue L., 1987, In: Current Communications in Molecular Biology, Cold Spring Harbor Laboratory ed.).

Transformation of a host cell with recombinant DNA may be carried out by conventional techniques as are well known to those skilled in the art. Where the host is prokaryotic, such as *E. coli*, competent cells which are capable of DNA uptake can be prepared from cells harvested after exponential growth phase and subsequently treated by the $CaCl_2$ method using procedures well known in the art. Alternatively, $MgCl_2$ or RbCl can be used. Transformation can also be performed after forming a protoplast of the host cell if desired.

When the host is a eukaryote, such methods of transfection of DNA as calcium phosphate co-precipitates, conventional mechanical procedures such as microinjection, electroporation, insertion of a plasmid encased in liposomes, or virus vectors may be used. Eukaryotic cells can also be cotransformed with DNA sequences encoding the JAK3 of the invention, and a second foreign DNA molecule encoding a selectable phenotype, such as the herpes simplex thymidine kinase gene. Another method is to use a eukaryotic viral vector, such as simian virus 40 (SV40) or bovine papilloma virus, to transiently infect or transform eukaryotic cells and express the protein. (see for example, *Eukaryotic Viral Vectors*, Cold Spring Harbor Laboratory, Gluzman ed., 1982).

Isolation and purification of microbial expressed polypeptide, or fragments thereof, provided by the invention, may be carried out by conventional means including preparative chromatography and immunological separations involving monoclonal or polyclonal antibodies.

The invention includes antibodies immunoreactive with or which bind to JAK3 polypeptide or functional fragments thereof. Antibody which consists essentially of

pooled monoclonal antibodies with different epitopic specificities, as well as distinct monoclonal antibody preparations are provided. Monoclonal antibodies are made from antigen containing fragments of the protein by methods well known to those skilled in the art (Kohler, *et al., Nature*, 256:495, 1975). The term antibody as used in this invention is meant to include intact molecules as well as fragments thereof, such as Fab and $F(ab')_2$, which are capable of binding an epitopic determinant on JAK3. The antibodies of the invention include antibodies which bind to the polypeptide of SEQ ID NO:2 and which bind with immunoreactive fragments of SEQ ID NO:2.

The term "antibody" as used in this invention includes intact molecules as well as fragments thereof, such as Fab, $F(ab')_2$, and Fv which are capable of binding the epitopic determinant. These antibody fragments retain some ability to selectively bind with its antigen or receptor and are defined as follows:

(1) Fab, the fragment which contains a monovalent antigen-binding fragment of an antibody molecule can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain;

(2) Fab', the fragment of an antibody molecule can be obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain; two Fab' fragments are obtained per antibody molecule;

(3) $(Fab')_2$, the fragment of the antibody that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction; $F(ab')_2$ is a dimer of two Fab' fragments held together by two disulfide bonds;

(4) Fv, defined as a genetically engineered fragment containing the variable genetically fused single chain molecule.

Methods of making these fragments are known in the art. (See for example, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, New York (1988), incorporated herein by reference).

As used in this invention, the term "epitope" means any antigenic determinant on an antigen to which the paratope of an antibody binds. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics.

Antibodies which bind to the JAK3 polypeptide of the invention can be prepared using an intact polypeptide or fragments containing small peptides of interest as the immunizing antigen. The polypeptide such as SEQ ID NO:2 used to immunize an animal can be derived from translated cDNA or chemical synthesis which can be conjugated to a carrier protein, if desired. Such commonly used carriers which are chemically coupled to the peptide include keyhole limpet hemocyanin (KLH), thyroglobulin, bovine serum albumin (BSA), and tetanus toxoid. The coupled peptide is then used to immunize the animal (e.g., a mouse, a rat, or a rabbit).

If desired, polyclonal or monoclonal antibodies can be further purified, for example, by binding to and elution from a matrix to which the polypeptide or a peptide to which the antibodies were raised is bound. Those of skill in the art will know of various techniques common in the immunology arts for purification and/or concentration of polyclonal antibodies, as well as monoclonal antibodies (See for example, Coligan, *et al.*, Unit 9, *Current Protocols in Immunology*, Wiley Interscience, 1991, incorporated by reference).

It is also possible to use the anti-idiotype technology to produce monoclonal antibodies which mimic an epitope. For example, an anti-idiotypic monoclonal antibody made to a first monoclonal antibody will have a binding domain in the hypervariable region which is the "image" of the epitope bound by the first monoclonal antibody.

The invention also provides a method for detecting a cell proliferative disorder associated with JAK3 in a subject, comprising contacting a target cellular component containing JAK3, with a reagent which detects JAK3. The target cell component can be nucleic acid, such as DNA or RNA, or it can be protein. When the component is nucleic acid, the reagent is a nucleic acid probe or PCR primer. When the cell component is protein, the reagent is an antibody probe. The probes can be detectably labeled, for example, with a radioisotope, a fluorescent compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator, or an enzyme. Those of ordinary skill in the art will know of other suitable labels for binding to the antibody, or will be able to ascertain such, using routine experimentation.

For purposes of the invention, an antibody or nucleic acid probe specific for JAK3 may be used to detect the presence of JAK3 polypeptide (using antibody) or polynucleotide (using nucleic acid probe) in biological fluids or tissues. Oligonucleotide primers based on any coding sequence region in the JAK3 sequence are useful for amplifying DNA, for example by PCR. Any specimen containing a detectable amount of polynucleotide or antigen can be used. A preferred sample of this invention is blood or a tissue of liver, lung, kidney, spleen and intestine. Preferably the subject is human. When the cell proliferative disorder associated with JAK3 is a hematopoietic cell disorder, it may include leukemia, myelodysplasia, polyethemia vera, thrombocytosis and aplastic anemia, for example.

Monoclonal antibodies used in the method of the invention are suited for use, for example, in immunoassays in which they can be utilized in liquid phase or bound to a solid phase carrier. In addition, the monoclonal antibodies in these immunoassays can be detectably labeled in various ways. Examples of types of immunoassays which can utilize monoclonal antibodies of the invention are competitive and non-competitive immunoassays in either a direct or indirect format. Examples of such immunoassays are the radioimmunoassay (RIA) and the sandwich (immunometric) assay. Detection of the antigens using the monoclonal antibodies of the invention can be done utilizing immunoassays which are run in either the forward, reverse, or simultaneous modes, including immunohistochemical assays on physiological

samples. Those of skill in the art will know, or can readily discern, other immunoassay formats without undue experimentation.

The term "immunometric assay" or "sandwich immunoassay", includes simultaneous sandwich, forward sandwich and reverse sandwich immunoassays. These terms are well understood by those skilled in the art. Those of skill will also appreciate that antibodies according to the present invention will be useful in other variations and forms of assays which are presently known or which may be developed in the future. These are intended to be included within the scope of the present invention.

Monoclonal antibodies can be bound to many different carriers and used to detect the presence of JAK3 polypeptide. Examples of well-known carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, agaroses and magnetite. The nature of the carrier can be either soluble or insoluble for purposes of the invention. Those skilled in the art will know of other suitable carriers for binding monoclonal antibodies, or will be able to ascertain such using routine experimentation.

In performing the assays it may be desirable to include certain "blockers" in the incubation medium (usually added with the labeled soluble antibody). The "blockers" are added to assure that non-specific proteins, proteases, or anti-heterophilic immunoglobulins to anti-JAK3 immunoglobulins present in the experimental sample do not cross-link or destroy the antibodies on the solid phase support, or the radiolabeled indicator antibody, to yield false positive or false negative results. The selection of "blockers" therefore may add substantially to the specificity of the assays described in the present invention.

It has been found that a number of nonrelevant (i.e., nonspecific) antibodies of the same class or subclass (isotype) as those used in the assays (e.g., IgG1, IgG2a, IgM, etc.) can be used as "blockers". The concentration of the "blockers" (normally 1-100 μg/μl) may be important, in order to maintain the proper sensitivity yet inhibit any unwanted interference by mutually occurring cross reactive proteins in the specimen.

In using a monoclonal antibody for the *in vivo* detection of antigen, the detectably labeled monoclonal antibody is given in a dose which is diagnostically effective. The term "diagnostically effective" means that the amount of detectably labeled monoclonal antibody is administered in sufficient quantity to enable detection of the site having the JAK3 antigen for which the monoclonal antibodies are specific.

The concentration of detectably labeled monoclonal antibody which is administered should be sufficient such that the binding to those cells having JAK3 is detectable compared to the background. Further, it is desirable that the detectably labeled monoclonal antibody be rapidly cleared from the circulatory system in order to give the best target-to-background signal ratio.

As a rule, the dosage of detectably labeled monoclonal antibody for *in vivo* diagnosis will vary depending on such factors as age, sex, and extent of disease of the individual. The dosage of monoclonal antibody can vary from about 0.001 mg/m^2 to about 500 mg/m^2, preferably 0.1 mg/m^2 to about 200 mg/m^2, most preferably about 0.1 mg/m^2 to about 10 mg/m^2. Such dosages may vary, for example, depending on whether multiple injections are given, tumor burden, and other factors known to those of skill in the art.

For *in vivo* diagnostic imaging, the type of detection instrument available is a major factor in selecting a given radioisotope. The radioisotope chosen must have a type of decay which is detectable for a given type of instrument. Still another important factor in selecting a radioisotope for *in vivo* diagnosis is that the half-life of the radioisotope be long enough so that it is still detectable at the time of maximum uptake by the target, but short enough so that deleterious radiation with respect to the host is minimized. Ideally, a radioisotope used for *in vivo* imaging will lack a particle emission, but produce a large number of photons in the 140-250 keV range, which may be readily detected by conventional gamma cameras.

For *in vivo* diagnosis, radioisotopes may be bound to immunoglobulin either directly or indirectly by using an intermediate functional group. Intermediate functional

groups which often are used to bind radioisotopes which exist as metallic ions to immunoglobulins are the bifunctional chelating agents such as diethylenetriaminepentacetic acid (DTPA) and ethylenediaminetetraacetic acid (EDTA) and similar molecules. Typical examples of metallic ions which can be bound to the monoclonal antibodies of the invention are ^{111}In, ^{97}Ru, ^{67}Ga, ^{68}Ga, ^{72}As, ^{89}Zr, and ^{201}Tl.

A monoclonal antibody useful in the method of the invention can also be labeled with a paramagnetic isotope for purposes of *in vivo* diagnosis, as in magnetic resonance imaging (MRI) or electron spin resonance (ESR). In general, any conventional method for visualizing diagnostic imaging can be utilized. Usually gamma and positron emitting radioisotopes are used for camera imaging and paramagnetic isotopes for MRI. Elements which are particularly useful in such techniques include ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Cr, and ^{56}Fe.

The present invention also provides a method for treating a subject with a cell proliferative disorder associated with JAK3 comprising administering to a subject with the disorder a therapeutically effective amount of reagent which modulates JAK3. In hematopoietic cancers, for example, the JAK3 nucleotide sequence may be under-expressed as compared to expression in a normal cell, therefore, it is possible to design appropriate therapeutic or diagnostic techniques directed to this sequence. Thus, where a cell-proliferative disorder is associated with the expression of JAK3 associated with malignancy, nucleic acid sequences that modulate JAK3 expression at the transcriptional or translational level can be used. In cases when a cell proliferative disorder or abnormal cell phenotype is associated with the under expression of JAK3, for example, nucleic acid sequences encoding JAK3 (sense) could be administered to the subject with the disorder.

The term "cell-proliferative disorder" denotes malignant as well as non-malignant cell populations which often appear to differ from the surrounding tissue both morphologically and genotypically. Such disorders may be associated, for example, with absence of expression of JAK3. Essentially, any disorder which is etiologically linked to

expression of JAK3 could be considered susceptible to treatment with a reagent of the invention which modulates JAK3 expression.

The term "modulate" envisions the suppression of JAK3 gene expression when JAK3 is over-expressed. When JAK3 is over-expressed, an antisense polynucleotide for JAK3 can be introduced into the cell. Alternatively, when a cell proliferative disorder is associated with under-expression of JAK3 polypeptide, a sense polynucleotide sequence (the DNA coding strand) encoding JAK3 polypeptide can be introduced into the cell. The term "therapeutically effective" amount refers to that amount of reagent includes that amount which modulates JAK3 expression o kinase activity such that the symptoms of the disorder are reduced.

The present invention also provides gene therapy for the treatment of cell proliferative disorders which are mediated by JAK3. Such therapy would achieve its therapeutic effect by introduction of the appropriate JAK3 polynucleotide which contains a JAK3 gene (sense), into cells of subjects having the proliferative disorder. Delivery of sense JAK3 polynucleotide constructs can be achieved using a recombinant expression vector such as a chimeric virus or a colloidal dispersion system. An expression vector including the JAK3 polynucleotide sequence could be introduced to the subject's cells *ex vivo* after removing, for example, stem cells from a subject's bone marrow. The cells are then reintroduced into the subject, (*e.g.*, into subject's bone marrow).

Various viral vectors which can be utilized for gene therapy as taught herein include adenovirus, herpes virus, vaccinia, or, preferably, an RNA virus such as a retrovirus. Preferably, the retroviral vector is a derivative of a murine or avian retrovirus. Examples of retroviral vectors in which a single foreign gene can be inserted include, but are not limited to: Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), and Rous Sarcoma Virus (RSV), and gibbon ape leukemia virus (GaLV), which provides a broader host range than many of the murine viruses. A number of additional retroviral vectors can incorporate multiple genes. All of these vectors can transfer or incorporate a gene for a selectable marker so that transduced cells can be identified

and generated. By inserting a JAK3 sequence (including promoter region) of interest into the viral vector, along with another gene which encodes the ligand for a receptor on a specific target cell, for example, the vector is now target specific. Preferred targeting is accomplished by using an antibody to target the retroviral vector. Those of skill in the art will know of, or can readily ascertain without undue experimentation, specific polynucleotide sequences which can be inserted into the retroviral genome to allow target specific delivery of the retroviral vector containing the JAK3 sense or antisense polynucleotide.

Since recombinant retroviruses are defective, they require assistance in order to produce infectious vector particles. This assistance can be provided, for example, by using helper cell lines that contain plasmids encoding all of the structural genes of the retrovirus under the control of regulatory sequences within the LTR. These plasmids are missing a nucleotide sequence which enables the packaging mechanism to recognize an RNA transcript for encapsidation. Helper cell lines which have deletions of the packaging signal include but are not limited to Ψ2, PA317 and PA12, for example. These cell lines produce empty virions, since no genome is packaged. If a retroviral vector is introduced into such cells in which the packaging signal is intact, but the structural genes are replaced by other genes of interest, the vector can be packaged and vector virion produced.

Another targeted delivery system for JAK3 polynucleotide is a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. The preferred colloidal system of this invention is a liposome. Liposomes are artificial membrane vesicles which are useful as delivery vehicles *in vitro* and *in vivo*. It has been shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0 um can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, DNA and intact virions can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, *et al.*, *Trends Biochem. Sci.*, 6:77, 1981). In addition to mammalian cells, liposomes have been used for delivery

of polynucleotides in plant, yeast and bacterial cells. In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: (1) encapsulation of the genes of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, *et al.*, *Biotechniques*, 6:682, 1988).

The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

Examples of lipids useful in liposome production include phosphatidyl compounds, such as phosphatidylglycerol, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, sphingolipids, cerebrosides, and gangliosides. Particularly useful are diacylphosphatidylglycerols, where the lipid moiety contains from 14-18 carbon atoms, particularly from 16-18 carbon atoms, and is saturated. Illustrative phospholipids include egg phosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

The targeting of liposomes has been classified based on anatomical and mechanistic factors. Anatomical classification is based on the level of selectivity, for example, organ-specific, cell-specific, and organelle-specific. Mechanistic targeting can be distinguished based upon whether it is passive or active. Passive targeting utilizes the natural tendency of liposomes to distribute to cells of the reticulo-endothelial system (RES) in organs which contain sinusoidal capillaries. Active targeting, on the other hand, involves alteration of the liposome by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein, or by changing the composition or size of the liposome in order to achieve targeting to organs and cell types other than the naturally occurring sites of localization.

The surface of the targeted delivery system may be modified in a variety of ways. In the case of a liposomal targeted delivery system, lipid groups can be incorporated into the lipid bilayer of the liposome in order to maintain the targeting ligand in stable association with the liposomal bilayer. Various linking groups can be used for joining the lipid chains to the targeting ligand.

In general, the compounds bound to the surface of the targeted delivery system will be ligands and receptors which will allow the targeted delivery system to find and "home in" on the desired cells. A ligand may be any compound of interest which will bind to another compound, such as a receptor.

In general, surface membrane proteins which bind to specific effector molecules are referred to as receptors. In the present invention, antibodies are preferred receptors. Antibodies can be used to target liposomes to specific cell-surface ligands. For example, certain antigens expressed specifically on tumor cells, referred to as tumor-associated antigens (TAAs), may be exploited for the purpose of targeting JAK3 antibody-containing liposomes directly to the malignant tumor. Since the JAK3 gene product may be indiscriminate with respect to cell type in its action, a targeted delivery system offers a significant improvement over randomly injecting non-specific liposomes. Preferably, the target tissue is human brain, colon, lung, and renal cancers. A number of procedures can be used to covalently attach either polyclonal or monoclonal antibodies to a liposome bilayer. Antibody-targeted liposomes can include monoclonal or polyclonal antibodies or fragments thereof such as Fab, or $F(ab')_2$, as long as they bind efficiently to an antigenic epitope on the target cells. Liposomes may also be targeted to cells expressing receptors for hormones or other serum factors.

For use in the diagnostic research and therapeutic applications suggested above, kits are also provided by the invention. The invention provides a diagnostic kit useful for the detection of a target cellular component indicative of a cell proliferative disorder associated with JAK3 comprising carrier means being compartmentalized to receive in close confinement therein one or more containers comprising a first container

containing a probe for detection of JAK3 nucleic acid. Such a kit may comprise a carrier means being compartmentalized to receive in close confinement one or more container means such as vials, tubes, and the like, each of the container means comprising one of the separate elements to be used in the method.

For example, one of the container means may comprise a probe which is or can be detectably labelled. Such probe may be an antibody or nucleotide specific for a target protein or a target nucleic acid, respectively, wherein the target is indicative, or correlates with, the presence of JAK3 of the invention. Where the kit utilizes nucleic acid hybridization to detect the target nucleic acid, the kit may also have containers containing nucleotide(s) for amplification of the target nucleic acid sequence and/or a container comprising a reporter-means, such as a biotin-binding protein, such as avidin or streptavidin, bound to a reporter molecule, such as an enzymatic, florescent, or radionucleotide label.

The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only and are not intended to limit the scope of the invention.

EXAMPLE 1

CLONING AND SEQUENCING OF JAK3

In order to clone the cDNA for a new member of the JAK family of non-receptor protein tyrosine kinases, degenerate oligonucleotides corresponding to parts of the highly conserved tyrosine kinase domain were used to amplify first strand cDNA from oligo (dT) primed, reverse transcribed, CD34+ total RNA from normal human bone marrow.

1. *Bone Marrow Fractions.* Iliac crest bone marrow was aspirated from consenting adult volunteers under an IRB approved protocol. Mononuclear cells were separated by Ficoll-Hypaque (Pharmacia, Piscataway, NJ) density gradient separation. Cell subsets were purified by immunomagnetic separation (Strauss, L.C., *et al.*, *The*

American Journal of Pediatric Hematology/Oncology, 13:217, 1991, Civin, C.I., *et al, Bone Marrow Purging and Processing*, 1990). Positive selection of the CD34+ fraction was done by incubation of the mononuclear fraction with 0.5 ug CD34 (HPCA-1, Becton Dickinson, San Jose, CA) antibody per 10^6 cells for 30 minutes at 4^0C. Cells were washed twice in RPMI 1640 (Sigma, St. Louis, MO) then resuspended in RPMI-1640 containing 1% human serum albumin at 5×10^7 cells/ml and incubated with sheep anti-mouse IgG1 conjugated immunomagnetic microspheres for 30 minutes at 4^0C. The CD34+ bound cells were released from the microspheres by treatment with chymopapain (Chymodiactin TM, Boots USA, Lincolnshire IL; final concentration 200 U/ml, 15 min., RT). The microspheres were removed from the free (CD34+ enriched) cells using a magnetic particle concentrator (Dynal, Great Neck, NY). CD34+ cells were further purified to obtain CD34+/Lin- cells by negative selection as described by Gore (Gore, S.D. *et al., Blood,* 8:1681, 1991).

2. *Isolation of RNA*. Poly A+ RNA was isolated from human hematopoietic cell lines using the Mini Ribosep mRNA isolation kit (Becton Dickinson, San Jose, CA). Total RNA from bone marrow cells and hematopoietic cell lines was extracted using the guanidium thiocyanate method (Chomczynski, P. and Sacchi, N., *Anal Biochem.*, 162:156, 1987).

3. *Cloning of JAK3*. Total RNA isolated from CD34+ cells (see above) was reverse transcribed with Superscript Moloney murine-leukemia-virus reverse transcriptase (BRL, Gaithersburg, MD) using oligo d(T) (Boehringer Mannheim, Germany) for priming. PCR amplification was carried out using degenerate oligonucleotides based on the highly conserved sequence motifs VHRDLA (5' GTNCA(T,C)(T,C)(C,A) GNGA(T,C)(TN GC3') AND DVWSYG (5' CCC-(G,A)TAN(G,C)(A,T) CCA NAC (G,A)TC3') from the PTK catalytic domain (Wilks, A.F., *et al., Gene,* 85:67, 1989, Wilks, A.F., *Methods in Enzymology,* 200: 533, 1991). To facilitate subcloning of the amplified PCR products Not 1 and Sal 1 sites were included as part of the PCR primers.

The resultant 226 bp bands were isolated after electrophoresis in agarose gels and cloned into the Not 1/ Sal 1 sites of pBluescript II KS- (Stratagene, La Jolla, CA). After sequencing, products containing known tyrosine kinase motifs were compared to reported sequences using the NCBI BlastN program (Altschul, S.F., *et al.*, *Journal of Molecular Biology*, 215:403, 1990). The fragment did not match any other sequences in the databases but was most closely related to members of the JAK family of tyrosine kinases at 65-70% nucleic acid identity.

The conditions for RT-PCR and thermal RACE were carried out as described by Frohman (Frohman, M.A., *Methods in Enzymology*, 218:340, 1993). KG1a poly A+RNA was used as the substrate for RACE. The 5' and 3' ends of JAK3 were also amplified from normal human bone marrow cDNA isolated from a λgt10 human bone marrow library (Clonetech, Palo Alto, CA) using primers specific for JAK3 with primers specific for the arms of λgt10 under the same PCR conditions used for RACE.

4. *Sequencing of JAK3*. To correct for PCR errors, multiple overlapping partial clones of JAK3 isolated from KG1a and bone marrow cells were sequenced and compared using the dideoxy DNA sequencing method (USB, Cleveland, Ohio) (Sanger, F., *et al.*, *Proc. Natl. Acad. Sci. USA*, 74:5463, 1977). To verify some regions, RT PCR amplified fragments from normal human bone marrow and exon containing portions of normal human JAK3 P1 genomic clones (see below) were also sequenced.

5. *RNAse Protection Assays*. Efforts to obtain the full-length JAK3 clone by screening of several libraries proved unsuccessful. Therefore, RNAse protection assay were developed utilizing the initial PCR amplified kinase domain fragment to screen for leukemic derived cell lines expressing JAK3. RNAse protection assays were carried out using the MAXIscript T3 *in vitro* Transcription Kit (Ambion, Austin, Texas). Briefly, an anti-sense RNA probe was synthesized by runoff transcription using Bacteriophage T3 RNA polymerase on a pBluescript II KS- (Stratagene, La Jolla, CA) template linearized downstream of the JAK3 207 nucleotide PTK domain fragment. The resulting $^{32}P\alpha$-UTP labelled 249 base RNA probe was hybridized with

approximately 5μg of total RNA from hematopoietic cell lines and RNA from approximately equal numbers of cells from normal human bone marrow sub-fractions. RNA-RNA hybrids were treated with RNAse A and T, denatured and separated on an 8M-Urea, 6% acrylamide gel and exposed to film (Kodak X-OMAT) (Melton, D.A., *et al.*, *Nucleic Acids Research*, 12:7035, 1984). As an internal standard, a β-actin probe was also included with each hybridization reaction.

6. *JAK3 nucleotide and predicted amino acid sequence*: Of the cell lines tested in this initial screening, JAK3 was most highly expressed by the myeloblastic cell line KG1a. Thermal RACE and PCR was employed to cone the full-length cDNA of JAK3 from KG1a and normal human bone marrow cells (Frohman, M.A., *Therman RACE, Methods in Enzymology*, 218:340, 1993). Using several rounds of RACE we isolated 3,807 bp of JAK3 cDNA, a region which covers the entire predicted coding region for JAK3, 167 bases of 5' untranslated and 394 bases of 3' untranslated sequence. Figure 1 shows the nucleotide and predicted amino acid sequence of JAK3. The cDNA includes an open reading frame of 3,246 bases that predicts a protein of 1082 amino acids with a molecular weight of 121 kD. The putative initiating methionine shows the strongest homology with the Kozak consensus sequence (Kozak, M., *Nucleic Acids Research*, 15:8125, 1987). At the 3' end an in frame stop codon defines the C terminus of the JAK3 protein at position 3242.

EXAMPLE 2

SEQUENCE COMPARISON BETWEEN JAK3 AND OTHER JAK FAMILY MEMBER

1. *Amino acid comparison between JAK3 and other JAK family members*: T initial identification of JAK3 as the fourth member of the JAK family was based on a database search using the 207 bp PCR fragment. The comparison of full-length-JAK3 with the other JAK family members is shown in figure 2. Sequences of JAK family members were aligned using the Pileup program (GCG Company, Madison, WI). The numbering system begins with the initiating methionine of the JAK family

members. The numbering system does not take into account the insertion of gaps and, therefore, should be only regarded as a relative measure of location. The fifth line in the figure shows a consensus sequence derived if three out of four JAK family members have the identical amino acid in that position. Full-length JAK3 has 48% identity and 67% similarity with JAK2 (murine), 41% identity and 61% similarity with JAK1, and 40% identity and 60% similarity with TYK-2. In addition, recently, small fragments of tyrosine kinases by PCR approaches from a human breast cancer cell line (TK5) and rat brain (Ptk-2) have been isolated (Cance, W.G., *et al., Int. J. Cancer,* 54:571, 1993, Sánchez, M.P., *et al., Proc. Natl. Acad. Sci. USA,* 91:1819, 1994). Both of these TK's show 93% identity with JAK3 in this short region, while rat Jak3 shares 99% identity in this region. How JAK3 relates to these PTKs must await the isolation of their full coding regions.

2. *Amino acid comparison between JAK3 and rat JAK3*: Figure 3 shows the comparison of JAK3 with the recently reported rat Jak3. The sequences of human JAK3 and rat Jak3 were aligned using the Pileup program (GCG Company, Madison, WI) The amino acids of each member are numbered beginning with the initiating methionine. The comparison shows 77% identity and 84% similarity making it likely that these genes are homologies (Takahashi, T. and Shirasawa, T., *FEBS Letters,* 342:124, 1994).

EXAMPLE 3

CHARACTERIZATION OF JAK3 EXPRESSION

1. RNAse protection analysis of JAK3 expression in leukemic derived cell lines: To investigate the hematopoietic expression of JAK3, the RNAse protection assay was used utilizing the 206 bp PCR kinase domain fragment of JAK3 to screen leukemic derived cell lines (see above). Briefly, a 32P α-UTP labelled anti-sense RNA probe to the kinase domain of JAK3 was hybridized with 5ugs total RNA from hematopoietic cell lines. A ß-actin probe was also included with each reaction as an internal standard, with the exception of the bone marrow and ML-1 populations, which were separately assayed for JAK3 and actin. As shown in Figure 4a, a protected band migrating at the expected size is seen in a number of

lanes. Positive signals were discernable for the Molt-16, Molt-3, KG1, KG1a, PB697, Nalm-16, Nalm-6, and TF-1 cell lines. These positive cell lines represent various forms of leukemia; the Molt lines were derived from T-lineage ALL, the KG1 lines from AML, PB697 and the Nalm lines are B lineage ALL, and TF-1 was established from an erythroleukemia. No signals were seen from RNA derived from the ML-1, HL60, K562, or Daudi cell lines representing additional AML, APL, CML, and Burkitt's leukemia lines, respectively.

2. *Northern blot analysis of JAK3 expression in leukemic derived cell lines*: Although the coding region of the cDNAs for the JAK family are ~3400 bp, the 5' and 3' untranslated regions and polyadenylation result in transcripts ranging from 4.4 kbp for JAK1, 4.8kbp for JAK2, 5.4 kbp for TYK-2 and 4.0 kbp for rat Jak3. To investigate the size of JAK3 message, a Northern blot with poly A+ RNA isolated from a number of hematopoietic cell lines was probed with a 1.8 kbp JAK3 fragment. 5 μg of poly A+ RNA samples from hematopoietic cell lines were incubated at 55°C for 15 minutes with 50% formamide, 6.5% formaldehyde, and 1X MOPS. Following the addition of formaldehyde loading buffer and ethidium bromide, RNA samples were electrophoresed in a 1.2% agarose gel containing 1X MOPS and 11% formaldehyde. Following electrophoresis, gels were transferred by capillary action to nitrocellulose 47. Sambrook J., Fritsch E.F., Maniatis T.: Molecular Cloning. A Laboratory Manual. 1989). As is evident from figure 4b (upper half), JAK3 is not a very highly expressed message. Even after an exposure of 17 days at -80°C with two intensifying screens, signals were barely visible in the lanes containing RNA from the HEL, REH, KG1, and KG1a cell lines (HEL represents an erythroleukemia, REH is derived from a B-lineage ALL, and the KG1 and KG1a cell lines are myeloblastic). RNA markers give an estimate of 5.8 kbp for the JAK3 transcript in these cells.

3. *Northern blot analysis of JAK3 expression in non-hematopoietic tissues*: To assess the expression of JAK3 in non-hematopoietic normal adult tissues, a Northern blot containing 2μg of poly A+ RNA from human heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas was screened. (Clonetech, Palo

Alto, CA). Northern blots were prehybridized for 2 hrs in 50% formamide, 5x SSPE, 10x Denhardt's, 2% SDS, and 100 ug/ml denatured salmon sperm DNA (Clonetech). Blots were hybridized with a randomly primed ^{32}P-dCTP labeled probe corresponding to a 1.8 kbp fragment of JAK3 cDNA (Feinberg, A.P. and Vogelstein, B., *Anal. Biochem.*, 132:6, 1983). The blots were exposed to film (Kodak x-OMAT) for 1½ days at -80°C between two intensifying screens.

When the same JAK3 fragment was also used to probe a Northern blot containing RNA from non-hematopoietic human tissues (Figure 4c), signals are seen from placenta, lung, liver, kidney, and pancreas, all with a similar message size of 5.8 kbp with possibly an additional less distinct band at -7.5 kbp. Unlike rat JAK3, which is expressed in rat heart and brain, no signals were seen from the RNA representing heart, brain, or skeletal muscle.

4. *RNAse Protection of JAK3 expression in normal bone marrow fractions*: Although the initial JAK3 fragment was generated by PCR amplification of CD34+ enriched bone marrow RNA, it remained a possibility that JAK3 expression was restricted to contaminating CD34- cells. To determine which populations of normal bone marrow express JAK3, fractions representing whole BM, CD34+, CD34- (i.e. depleted of CD34+ cells), CD34+/lin-, as well as peripheral blood were isolated. RNA was then extracted and used to perform the RNAse protection assay. The same probe used in Figure 4a was hybridized with approximately 1-5 μgs of RNA from normal total bone marrow, bone marrow subfractions, and from peripheral blood. As an internal standard, a ß-actin probe was also included with each reaction as a standard for the amount and quality of RNA loaded in each sample. The presence of a band that migrates between the JAK3 and actin bands in all lanes, including the no RNA and tRNA control lanes, is a result of incomplete digestion of the probe. All of the sample lanes give a protected JAK3 band migrating at the expected size. However, probably because of the limited amounts of RNA obtained from several fractions, the actin bands indicate a variation in total RNA loaded for each sample.

To determine the relative expression of JAK3 in these different populations, the bands were quantified by phosphorimager scanning and normalized relative to the actin signal. Figure 5b shows the phosphorimage analysis of bone marrow fractions. Following exposure to film, the gel shown in Figure 5b was exposed to a phosphorimage screen (Molecular Dynamics, Sunnyvale, CA). Bands were quantified using the ImageQuantify program and normalized relative to the actin signals. Figure 5b shows the strongest relative signals result from the CD34+ RNA and the even more stem cell enriched CD34+/lin- RNA sample. Thus, JAK3 is most highly expressed in this primitive population of cells and may play a role in transducing the signal of receptor functioning in the proliferative, survival and/or developmental pathways of these cells. JAK3 is also expressed in the CD34- and peripheral blood fractions and is thus likely to be involved with a subset of receptors involved in differentiated cell signalling, in analogy to JAK1, JAK2, and TYK-2.

EXAMPLE 4
CHROMOSOMAL LOCALIZATION OF THE JAK3 GENE

1. *Somatic cell hybrid analysis.* To determine the chromosomal localization of the JAK3 gene, a human/rodent somatic cell hybrid mapping panel, NIGMS #2, which included human, mouse and hamster genomic DNA controls was screened by PCR (Drwinga, H., *et al.*, *Genomics*, 16:311, 1993, Dubois, B. and Naylor, S., *Genomics*, 16:315, 1993). In this panel, most of the somatic cell hybrid samples contained DNA from a single specific human chromosome in a rodent background. To preclude cDNA contamination problems, a primer pair was selected that resulted in a PCR product from genomic DNA that was larger than the produce resulting from cDNA due to the presence of intronic sequence. The plus strand oligo 5'AGCCGCCTCCTTCTCT3' (SEQ. ID NO:3) and minus strand oligo 5'CGGCAGCAGCTTAGCTAGG3' (SEQ. ID NO:4) amplify an approximate 410 base pair product from human genomic DNA and a 156 base pair product from JAK3 cDNA.

For PCR, 100 ngs of genomic DNA from each hybrid cell line were used as the target for amplification. PCR amplification was performed using the following parameters: (94°C, 1'-> 55°C, 1'-> 72°C,2') x 30 -> 72°C, 15'. The final concentrations of reagents were 0.2 mM dNTP, 50 mM KCL, 3.0 mM Mg, 0.1 U Taq Polymerase/ml, and 2.5 mM each primer. The results from the PCR amplification were confirmed by Southern transfer and hybridization with a ^{32}P γ-ATP kinase labelled oligo internal to the primers used for amplification.

Using the primer pair results in a PCR product only with DNA from human cells and not from mouse or hamster DNA . These oligonucleotides were then used on DNA samples from the library representing each of the human chromosomes. The amplified DNA was electrophoresed and after transfer to nitrocellulose was hybridized to a radiolabelled oligonucleotide internal to the other oligonucleotides used for the PCR. Only the DNA from a cell line containing human chromosome 19 gave a significant signal.

2. *Fluorescence in situ hybridization*: TYK-2 has also been mapped to chromosome 19 (JAK1 and JAK2 have been mapped to 1p31.3 and 9p24, respectively)[55,56] Several pairs of tyrosine kinases (eg. PDGFRβ and c-fms, PDGFα and c-kit, FLT3 and FLT1) have been shown to be closely linked, leading to the hypothesis that these receptor tyrosine kinases evolved by a trans duplication followed by a cis duplication.[57-60] In order to confirm the location of the gene on chromosome 19, to sublocalize the gene to a specific band, and to investigate the possibility that JAK3 and TYK-2 were linked, FISH experiment was carried out.

First clone containing approximately 80kbp of the JAK3 gene was isolated by PCR screening of a P1 library using the same oligonucleotides used above. Briefly, P1 genomic clones of JAK3 were obtained by PCR screening of the Du Pont Merck Pharmaceutical Company Human Foreskin Fibroblast P1 Library #1 (DMPC-HFF#1)(Genome Systems, St. Louis, MO). The clones were designated DMPC-HFF#1-1441, DMPC-HFF#1-1442, DMPC-HFF#1-1443 and identified using the same primer pairs and PCR conditions used for the screening of the human/rodent

somatic cell hybrid mapping panel (see above). Partial sequencing of these P1 clones has confirmed that they represent genomic JAK3 DNA.

The P1 vector containing the approximate 80 kbp genomic clone 1441 of JAK3 was nick-translated with biotin-14 dATP (BRL, Gaithersburg, MD), with 30% incorporation determined by tritium tracer incorporation. Slides with chromosome spreads were made from normal male lymphocytes cultured with BrdU (Bhatt, B., *et al., Nucleic Acids Res.*, 16:3951, 1988). Fluorescence in situ hybridization was performed as described by Lichter, et. al., (53. Lichter, P., Tang, C., Call, K., Hermanson, G., Evans, G., Housman, D., Ward, D.: High resolution mapping of human chromosome 11 by in situ hybridization with cosmid clones. *Science* 247:64, 1990) with modifications. Probe mix (2XSSCP, 60% formamide, 10% dextran sulfate, 4 ng/ul biotinylated probe, 300 ng/ul Cot-1 DNA (to suppress repeated sequences) and 150 ng/ul salmon sperm DNA was denatured at 70°C for 5 minutes, preannealed at 37°C for 40 minutes, placed on slides and hybridized at 37°C overnight. Slides were washed in 70% formamide/2XSSC at 43°C for 20 minutes, and 2 changes of 2xSSC at 37°C for 5 minutes each. Biotinylated probe was detected with FITC-avidin and amplified with biotinylated anti-avidin, using reagents from an in situ hybridization kit (Oncor Inc., Gaithersburg, MD), following the manufacturer's instructions.

Analysis of 36 metaphase cells showed 20 cells (56%) had at least one pair of signals (involving both chromatids of a single chromosome). These 20 metaphases were photographed on color slide film (Kodak Ekttachrome 400HC) and 33 paired signals were seen, with all but one located on the proximal short arm of an F-group (chr. 19 or 20) chromosome, an example of which is shown in Figure 6a. To determine the specific chromosome and band location of the signals, the hybridized slides were G-banded by FPG (fluorescence plus Giemsa), photographed, and aligned with the color slides to determine the subband location. Figure 6b shows the position of the paired FISH signals on the G-banded chromosomes. All 33 signals were analyzable after banding and all were on chromosome 19, with most on bands p12-13.1 (Figure 6c). Thus JAK3 may be located near TYK-2, which

has been localized to 19p13.2. Figure 6c is the ideogram of human chromosome 19, showing localization of JAK3 to 19p12-13.1. Each dot represents a paired signal seen on metaphase chromosomes. Signals clearly located on a single band are diagrammed to the right of the ideogram; those which could not be sublocalized to a single band are assigned to regions diagrammed to the left (brackets).

The foregoing is meant to illustrate, but not to limit, the scope of the invention. Indeed, those of ordinary skill in the art can readily envision and produce further embodiments, based on the teachings herein, without undue experimentation.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: The Johns Hopkins University School of Medicine

(ii) TITLE OF INVENTION: NOVEL PROTEIN TYROSINE KINASE, JAK3

(iii) NUMBER OF SEQUENCES: 12

(iv) CORRESPONDENCE ADDRESS:
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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: PCT/US95
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(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Haile, Lisa A.
(B) REGISTRATION NUMBER: 38,347
(C) REFERENCE/DOCKET NUMBER: 07265/033WO1

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 619/678-5070
(B) TELEFAX: 619/678-5099

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3807 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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AAACAGTTAA TACATATTTT TTATGTTACG TGTATTCTGT ACAACAAAGT AAGCTAGACA      60

AAAGAAAATG TTTTCTCCTT CCTGTGTGGG ACTTTCCTCT CGCTGCCTCC CGGCTCTGCC     120

CGCCCTTCGA AAGTCCAGGG TCCCTGCCCG CTAGGCAAGT TGCACTC ATG GCA CCT       176
                                                    Met Ala Pro
                                                      1

CCA AGT GAA GAG ACG CCC CTG ATC CCT CAG CGT TCA TGC AGC CTC TTG       224
Pro Ser Glu Glu Thr Pro Leu Ile Pro Gln Arg Ser Cys Ser Leu Leu
      5                  10                  15

TCC ACG GAG GCT GGT GCC CTG CAT GTG CTG CTG CCC GCT CGG GGC CCC       272
Ser Thr Glu Ala Gly Ala Leu His Val Leu Leu Pro Ala Arg Gly Pro
 20                  25                  30                  35
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GGG CCC CCC CAG CGC CTA TCT TTC TCC TTT GGG GAC CAC TTG GCT GAG        320
Gly Pro Pro Gln Arg Leu Ser Phe Ser Phe Gly Asp His Leu Ala Glu
                 40                  45                  50

GAC CTG TGC GTG CAG GCT GCC AAG GCC AGC GCG ATC CTG CCT GTG TAC        368
Asp Leu Cys Val Gln Ala Ala Lys Ala Ser Ala Ile Leu Pro Val Tyr
             55                  60                  65

CAC TCC CTC TTT GCT CTG GCC ACG GAG GAC CTG TCC TGC TGG TTC CCC        416
His Ser Leu Phe Ala Leu Ala Thr Glu Asp Leu Ser Cys Trp Phe Pro
         70                  75                  80

CGA GCC ACA TCT TCT CCG TGG AGG ATG CCA GCA CCC CAA GTC CTG CTG        464
Arg Ala Thr Ser Ser Pro Trp Arg Met Pro Ala Pro Gln Val Leu Leu
     85                  90                  95

TAC AGG ATT CGC TTT TAC TTC CCC AAT TGG TTT GGG CTG GAG AAG TGC        512
Tyr Arg Ile Arg Phe Tyr Phe Pro Asn Trp Phe Gly Leu Glu Lys Cys
100                 105                 110                 115

CAC CGC TTC GGG CTA CGC AAG GAT TTG GCC AGT GCT ATC CTT GAC CTG        560
His Arg Phe Gly Leu Arg Lys Asp Leu Ala Ser Ala Ile Leu Asp Leu
                120                 125                 130

CCA GTC CTG GAG CAC CTC TTT GCC CAG CAC CGC AGT GAC CTG GTG AGT        608
Pro Val Leu Glu His Leu Phe Ala Gln His Arg Ser Asp Leu Val Ser
            135                 140                 145

GGG CGC CTC CCC CGT GGC CTC AGT CTC AAG GAG CAG GGT GAG TGT CTC        656
Gly Arg Leu Pro Arg Gly Leu Ser Leu Lys Glu Gln Gly Glu Cys Leu
        150                 155                 160

AGC CTG GCC GTG TTG GAC CTG GCC CGG ATG GCG CGA GAG CAG GCC CAG        704
Ser Leu Ala Val Leu Asp Leu Ala Arg Met Ala Arg Glu Gln Ala Gln
    165                 170                 175

CGG CGG GGA GAG CTG CTG AAG ACT GTC AGC TAC AAG GCC TGC CTA CCC        752
Arg Arg Gly Glu Leu Leu Lys Thr Val Ser Tyr Lys Ala Cys Leu Pro
180                 185                 190                 195

CCA AGC CTG CGC GAC CTG ATC CAG GGC CTG AGC TTC GTG ACG GGG AGG        800
Pro Ser Leu Arg Asp Leu Ile Gln Gly Leu Ser Phe Val Thr Gly Arg
                200                 205                 210

CGT ATT CGG AGG ACG GTG GAG AGC CCC CTG CGC CGG GTG GCC GCC TGC        848
Arg Ile Arg Arg Thr Val Glu Ser Pro Leu Arg Arg Val Ala Ala Cys
            215                 220                 225

CAG GCA GAC CGG CAC TCG CTC ATG GCC AAG TAC ATC ATG GAC CTG GAG        896
Gln Ala Asp Arg His Ser Leu Met Ala Lys Tyr Ile Met Asp Leu Glu
        230                 235                 240

CGG CTG GAT CCA GCC GGG GCC GCC GAG ACC TTC CAC GTG GGC CTC CCT        944
Arg Leu Asp Pro Ala Gly Ala Ala Glu Thr Phe His Val Gly Leu Pro
    245                 250                 255

GGG GCC CTT GGT GGC CAC GAC GGG CTG GGG CTC GTC CGC GTG GCT GGT        992
Gly Ala Leu Gly Gly His Asp Gly Leu Gly Leu Val Arg Val Ala Gly
260                 265                 270                 275

GAC GGC GGC ATC GCC TGG ACC CAG GGA GAA CAG GAG GTC CTC CAG CCC       1040
Asp Gly Gly Ile Ala Trp Thr Gln Gly Glu Gln Glu Val Leu Gln Pro
                280                 285                 290

TTC TGC GAC TTT CCA GAA ATC GTA GAC ATT AGC ATC AAG CAG GCC CCG       1088
Phe Cys Asp Phe Pro Glu Ile Val Asp Ile Ser Ile Lys Gln Ala Pro
            295                 300                 305

CGC GTT GGC CCG GCC GGA GAG CAC CGC CTG GTC ACT GTT ACC AGG ACA       1136
Arg Val Gly Pro Ala Gly Glu His Arg Leu Val Thr Val Thr Arg Thr
        310                 315                 320
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GAC AAC CAG ATT TTA GAG GCC GAG TTC CCA GGG CTG CCC GAG GCT CTG 1184
Asp Asn Gln Ile Leu Glu Ala Glu Phe Pro Gly Leu Pro Glu Ala Leu
325 330 335

TCG TTC GTG GCG CTC GTG GAC GGC TAC TTC CGG CTG ACC ACG GAC TCC 1232
Ser Phe Val Ala Leu Val Asp Gly Tyr Phe Arg Leu Thr Thr Asp Ser
340 345 350 355

CAG CAC TTC TTC TGC AAG GAG GTG GAC CCG AGG CTG CTG GAG GAA GTG 1280
Gln His Phe Phe Cys Lys Glu Val Asp Pro Arg Leu Leu Glu Glu Val
360 365 370

GCC GAG CAG TGC CAC GGC CCC ATC ACT CTG GAC TTT GCC ATC AAC AAG 1328
Ala Glu Gln Cys His Gly Pro Ile Thr Leu Asp Phe Ala Ile Asn Lys
375 380 385

CTC AAG ACT GGG GGC TCA CGT CCT GGC TCC TAT GTT CTC CGC CGC ATC 1376
Leu Lys Thr Gly Gly Ser Arg Pro Gly Ser Tyr Val Leu Arg Arg Ile
390 395 400

CCC CAG GAC TTT GAC AGC TTC CTC CTC ACT GTC TGT GTC CAG AAC CCC 1424
Pro Gln Asp Phe Asp Ser Phe Leu Leu Thr Val Cys Val Gln Asn Pro
405 410 415

CTT GGT CCT GAT TAT AAG GGC TGC CTC ATC CGG CGC AGC CCC ACA GGA 1472
Leu Gly Pro Asp Tyr Lys Gly Cys Leu Ile Arg Arg Ser Pro Thr Gly
420 425 430 435

ACC TTC CTT CTG GTT GGC CTC AGC CGA CCC CAC AGC AGT CTT CGA GAG 1520
Thr Phe Leu Leu Val Gly Leu Ser Arg Pro His Ser Ser Leu Arg Glu
440 445 450

CTC CTG GCA ACC TGC TGG GAT GGG GGG CTG CAC GTA GAT GGG GTG GCA 1568
Leu Leu Ala Thr Cys Trp Asp Gly Gly Leu His Val Asp Gly Val Ala
455 460 465

GTG ACC CTC ACT TCC TGC TGT ATC CCC AGA CCC AAA GAA AAG TCC AAC 1616
Val Thr Leu Thr Ser Cys Cys Ile Pro Arg Pro Lys Glu Lys Ser Asn
470 475 480

CTG ATT GTG GTC CAG AGA GGT CAC AGC CCA CCC ACA TCA TCC TTG GTT 1664
Leu Ile Val Val Gln Arg Gly His Ser Pro Pro Thr Ser Ser Leu Val
485 490 495

CAG CCC CAA TCC CAA TAC CAG CTG AGT CAG ATG ACA TTT CAC AAG ATC 1712
Gln Pro Gln Ser Gln Tyr Gln Leu Ser Gln Met Thr Phe His Lys Ile
500 505 510 515

CCT GCT GAC AGC CTG GAG TGG CAT GAG AAC CTG GGC CAT GGG TCC TTC 1760
Pro Ala Asp Ser Leu Glu Trp His Glu Asn Leu Gly His Gly Ser Phe
520 525 530

ACC AAG ATT TAC CGG GGC TGT CGC CAT GAG GTG GTG GAT GGG GAG GCC 1808
Thr Lys Ile Tyr Arg Gly Cys Arg His Glu Val Val Asp Gly Glu Ala
535 540 545

CGA AAG ACA GAG GTG CTG CTG AAG GTC ATG GAT GCC AAG CAC AAG AAC
1856
Arg Lys Thr Glu Val Leu Leu Lys Val Met Asp Ala Lys His Lys Asn
550 555 560

TGC ATG GAG TCA TTC CTG GAA GCA GCG AGC TTG ATG AGC CAA GTG TCG 1904
Cys Met Glu Ser Phe Leu Glu Ala Ala Ser Leu Met Ser Gln Val Ser
565 570 575

TAC CGG CAT CTC GTG CTG CTC CAC GGC GTG TGC ATG GCT GGA GAC AGC 1952
Tyr Arg His Leu Val Leu Leu His Gly Val Cys Met Ala Gly Asp Ser
580 585 590 595

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ACC ATG GTC GAG GAA TTT GTA CAC CTG GGG GCC ATA GAC ATG TAT CTG      2000
Thr Met Val Glu Glu Phe Val His Leu Gly Ala Ile Asp Met Tyr Leu
            600                 605                 610

CGA AAA CGT GGC CAC CTG GTG CCA GCC AGC TGG AAG CTG CAG GTG GTC      2048
Arg Lys Arg Gly His Leu Val Pro Ala Ser Trp Lys Leu Gln Val Val
        615                 620                 625

AAA CAG CTG GCC TAC GCC CTC AAC TAT CTG GAG GAC AAA GGC CTG TCC      2096
Lys Gln Leu Ala Tyr Ala Leu Asn Tyr Leu Glu Asp Lys Gly Leu Ser
    630                 635                 640

CAT GGC AAT GTC TCT GCC CGG AAG GTG CTC CTG GCT CGG GAG GGG GCT      2144
His Gly Asn Val Ser Ala Arg Lys Val Leu Leu Ala Arg Glu Gly Ala
645                 650                 655

GAT GGG AGC CCG CCC TTC ATC AAG CTG AGT GAC CCT GGG GTC AGC CCC      2192
Asp Gly Ser Pro Pro Phe Ile Lys Leu Ser Asp Pro Gly Val Ser Pro
660                 665                 670                 675

GCT GTG TTA AGC CTG GAG ATG CTC ACC GAC AGG ATC CCC TGG GTG GCC      2240
Ala Val Leu Ser Leu Glu Met Leu Thr Asp Arg Ile Pro Trp Val Ala
            680                 685                 690

CCC GAG TGT CTC CGG GAG GCG CAG ACA CTT AGC TTG GAA GCT GAC AAG      2288
Pro Glu Cys Leu Arg Glu Ala Gln Thr Leu Ser Leu Glu Ala Asp Lys
        695                 700                 705

TGG GGC TTC GGC GCC ACG GTC TGG GAA GTG TTT AGT GGC GTC ACC ATG      2336
Trp Gly Phe Gly Ala Thr Val Trp Glu Val Phe Ser Gly Val Thr Met
    710                 715                 720

CCC ATC AGT GCC CTA GAT CCT GCT AAG AAA CTC CAA TTT TAT GAG GAC      2384
Pro Ile Ser Ala Leu Asp Pro Ala Lys Lys Leu Gln Phe Tyr Glu Asp
725                 730                 735

CGG CAG CAG CTG TCG GCC CCC AAG TGG ACA GAG CTG GCC CTG CTG ATT      2432
Arg Gln Gln Leu Ser Ala Pro Lys Trp Thr Glu Leu Ala Leu Leu Ile
740                 745                 750                 755

CAA CAG TGC ATG GCC TAT GAG CCG GTC CAG AGG CCC TCC TTA CGA GCC      2480
Gln Gln Cys Met Ala Tyr Glu Pro Val Gln Arg Pro Ser Leu Arg Ala
            760                 765                 770

GTC ATT CGT GAC CTC AAT AGT CTC ATC TCT TCA GAC TAT GAG CTC CTC      2528
Val Ile Arg Asp Leu Asn Ser Leu Ile Ser Ser Asp Tyr Glu Leu Leu
        775                 780                 785

TCA GAC CAC ACC TGG TGC CCT GGC ACT CGT GAT GGG CTG TGG AAT GGT      2576
Ser Asp His Thr Trp Cys Pro Gly Thr Arg Asp Gly Leu Trp Asn Gly
    790                 795                 800

GCC CAG CTC TAT GCC TGC CAA GAC CCC ACG ATC TTC GAG GAG AGA CAC      2624
Ala Gln Leu Tyr Ala Cys Gln Asp Pro Thr Ile Phe Glu Glu Arg His
805                 810                 815

CTC AAG TAC ATC TCA CAG CTG GGC AAG GGC TTC TTT GGC AGC GTG GAG      2672
Leu Lys Tyr Ile Ser Gln Leu Gly Lys Gly Phe Phe Gly Ser Val Glu
820                 825                 830                 835

CTG TGC CGC TAT GAC CCG CTA GGC GAC AAT ACA GGT GCC CTG GTG GCC      2720
Leu Cys Arg Tyr Asp Pro Leu Gly Asp Asn Thr Gly Ala Leu Val Ala
            840                 845                 850

GTG AAA CAG CTG CAG CAC AGC GGG CCA GAC CAG CAG AGG GAC TTT CAG
2768
Val Lys Gln Leu Gln His Ser Gly Pro Asp Gln Gln Arg Asp Phe Gln
        855                 860                 865
```

CGG GAG ATT CAG ATC CTC AAA GCA CAG CAC AGT GAT TTC ATT GTC AAG 2816
Arg Glu Ile Gln Ile Leu Lys Ala Gln His Ser Asp Phe Ile Val Lys
870 875 880

TAT CGT GGT GTC AGC TAT GGC CCG GGC CGC CAG AGC CCT GCG CTG GTC 2864
Tyr Arg Gly Val Ser Tyr Gly Pro Gly Arg Gln Ser Pro Ala Leu Val
885 890 895

ATG GAG TAC CTG CCC AGC GGC TGC TTG CGC GAC TTC CTG CAG CGG CAC 2912
Met Glu Tyr Leu Pro Ser Gly Cys Leu Arg Asp Phe Leu Gln Arg His
900 905 910 915

CGG GGC CTC GAT GCC AGC CGC CTC CTT CTC TAT TCC TCG CAG ATC TGC 2960
Arg Gly Leu Asp Ala Ser Arg Leu Leu Leu Tyr Ser Ser Gln Ile Cys
920 925 930

AAG GGC ATG GAG TAC CTG GGC TCC CGC CGC TGC GTG CAC CGC GAC CTG 3008
Lys Gly Met Glu Tyr Leu Gly Ser Arg Arg Cys Val His Arg Asp Leu
935 940 945

GCC GCC CGA AAC ATC CTC GTG GAG AGC GAG GCA CAC GTC AAG ATC GCT 3056
Ala Ala Arg Asn Ile Leu Val Glu Ser Glu Ala His Val Lys Ile Ala
950 955 960

GAC TTC GGC CTA GCT AAG CTG CTG CCG CTT GAC AAA GAC TAC TAC GTG 3104
Asp Phe Gly Leu Ala Lys Leu Leu Pro Leu Asp Lys Asp Tyr Tyr Val
965 970 975

GTC CGC GAG CCA GGC CAG AGC CCC ATT TTC TGG TAT GCC CCC GAA TCC 3152
Val Arg Glu Pro Gly Gln Ser Pro Ile Phe Trp Tyr Ala Pro Glu Ser
980 985 990 995

CTC TCG GAC AAC ATC TTC TCT CGC CAG TCA GAC GTC TGG AGC TTC GGG 3200
Leu Ser Asp Asn Ile Phe Ser Arg Gln Ser Asp Val Trp Ser Phe Gly
1000 1005 1010

GTC GTC CTG TAC GAG CTC TTC ACC TAC TGC GAC AAA AGC TGC AGC CCC 3248
Val Val Leu Tyr Glu Leu Phe Thr Tyr Cys Asp Lys Ser Cys Ser Pro
1015 1020 1025

TCG GCC GAG TTC CTG CGG ATG ATG GGA TGT GAG CGG GAT GTC CCC CGC 3296
Ser Ala Glu Phe Leu Arg Met Met Gly Cys Glu Arg Asp Val Pro Arg
1030 1035 1040

CTC TGC CGC CTC TTG GAA CTG CTG GAG GAG GGC CAG AGG CTG CCG GCG 3344
Leu Cys Arg Leu Leu Glu Leu Leu Glu Glu Gly Gln Arg Leu Pro Ala
1045 1050 1055

CCT CCT TGC TGC CCT GC TGAGGTGAGT TGCTACAGTG GCTGGAGAGA 3391
Pro Pro Cys Cys Pro
1060

CGACATCTGC CTGCCTGCTG AGTGAGTTGC TACAGTGGCT GAGAGACGAC ATCTGCTCCA 3451

TGGCTGGTGG CCGACAGTAA TCTCACGCCG GACCTGCCGC AGCCCCTGCC CCAGACCTCT 3511

CACCATCACC GCCACCACCG TGCAGCTGCC ACCAACCCTG CACGCTACTG CTGCCTCAGT 3571

GGCTGTACCC AACAAGACCT GCTGACCCTC TGTCGCTACT GATTCCTCCT TGGGTGCAGC 3631

CTCAGAGTGC CTGAGGCCCA GAGGGTCTGG TCTGGTGAGC TCCTGAGGCC ACACAGCACC 3691

ATAAAGTCTC GCATCTACAG GCCTTTGATT ACCTCCTGGG ATGGGTGCTC ACTATCTACC 3751

CCAGACCAAC GCCACCTGCA GCCTGTGGAG TCAACTGCAG AATAAATCAC ACCCTA 3807

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1064 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Ala Pro Pro Ser Glu Glu Thr Pro Leu Ile Pro Gln Arg Ser Cys
1 5 10 15

Ser Leu Leu Ser Thr Glu Ala Gly Ala Leu His Val Leu Leu Pro Ala
20 25 30

Arg Gly Pro Gly Pro Pro Gln Arg Leu Ser Phe Ser Phe Gly Asp His
35 40 45

Leu Ala Glu Asp Leu Cys Val Gln Ala Ala Lys Ala Ser Ala Ile Leu
50 55 60

Pro Val Tyr His Ser Leu Phe Ala Leu Ala Thr Glu Asp Leu Ser Cys
65 70 75 80

Trp Phe Pro Arg Ala Thr Ser Ser Pro Trp Arg Met Pro Ala Pro Gln
85 90 95

Val Leu Leu Tyr Arg Ile Arg Phe Tyr Phe Pro Asn Trp Phe Gly Leu
100 105 110

Glu Lys Cys His Arg Phe Gly Leu Arg Lys Asp Leu Ala Ser Ala Ile
115 120 125

Leu Asp Leu Pro Val Leu Glu His Leu Phe Ala Gln His Arg Ser Asp
130 135 140

Leu Val Ser Gly Arg Leu Pro Arg Gly Leu Ser Leu Lys Glu Gln Gly
145 150 155 160

Glu Cys Leu Ser Leu Ala Val Leu Asp Leu Ala Arg Met Ala Arg Glu
165 170 175

Gln Ala Gln Arg Arg Gly Glu Leu Leu Lys Thr Val Ser Tyr Lys Ala
180 185 190

Cys Leu Pro Pro Ser Leu Arg Asp Leu Ile Gln Gly Leu Ser Phe Val
195 200 205

Thr Gly Arg Arg Ile Arg Arg Thr Val Glu Ser Pro Leu Arg Arg Val
210 215 220

Ala Ala Cys Gln Ala Asp Arg His Ser Leu Met Ala Lys Tyr Ile Met
225 230 235 240

Asp Leu Glu Arg Leu Asp Pro Ala Gly Ala Ala Glu Thr Phe His Val
245 250 255

Gly Leu Pro Gly Ala Leu Gly Gly His Asp Gly Leu Gly Leu Val Arg
260 265 270

Val Ala Gly Asp Gly Gly Ile Ala Trp Thr Gln Gly Glu Gln Glu Val
275 280 285

Leu Gln Pro Phe Cys Asp Phe Pro Glu Ile Val Asp Ile Ser Ile Lys
290 295 300

Gln Ala Pro Arg Val Gly Pro Ala Gly Glu His Arg Leu Val Thr Val
305 310 315 320

Thr Arg Thr Asp Asn Gln Ile Leu Glu Ala Glu Phe Pro Gly Leu Pro
325 330 335

Glu Ala Leu Ser Phe Val Ala Leu Val Asp Gly Tyr Phe Arg Leu Thr
340 345 350

Thr Asp Ser Gln His Phe Phe Cys Lys Glu Val Asp Pro Arg Leu Leu
355 360 365

Glu Glu Val Ala Glu Gln Cys His Gly Pro Ile Thr Leu Asp Phe Ala
370 375 380

Ile Asn Lys Leu Lys Thr Gly Gly Ser Arg Pro Gly Ser Tyr Val Leu
385 390 395 400

Arg Arg Ile Pro Gln Asp Phe Asp Ser Phe Leu Leu Thr Val Cys Val
405 410 415

Gln Asn Pro Leu Gly Pro Asp Tyr Lys Gly Cys Leu Ile Arg Arg Ser
420 425 430

Pro Thr Gly Thr Phe Leu Leu Val Gly Leu Ser Arg Pro His Ser Ser
435 440 445

Leu Arg Glu Leu Leu Ala Thr Cys Trp Asp Gly Gly Leu His Val Asp
450 455 460

Gly Val Ala Val Thr Leu Thr Ser Cys Cys Ile Pro Arg Pro Lys Glu
465 470 475 480

Lys Ser Asn Leu Ile Val Val Gln Arg Gly His Ser Pro Pro Thr Ser
485 490 495

Ser Leu Val Gln Pro Gln Ser Gln Tyr Gln Leu Ser Gln Met Thr Phe
500 505 510

His Lys Ile Pro Ala Asp Ser Leu Glu Trp His Glu Asn Leu Gly His
515 520 525

Gly Ser Phe Thr Lys Ile Tyr Arg Gly Cys Arg His Glu Val Val Asp
530 535 540

Gly Glu Ala Arg Lys Thr Glu Val Leu Leu Lys Val Met Asp Ala Lys
545 550 555 560

His Lys Asn Cys Met Glu Ser Phe Leu Glu Ala Ala Ser Leu Met Ser
565 570 575

Gln Val Ser Tyr Arg His Leu Val Leu Leu His Gly Val Cys Met Ala
580 585 590

Gly Asp Ser Thr Met Val Glu Glu Phe Val His Leu Gly Ala Ile Asp
595 600 605

Met Tyr Leu Arg Lys Arg Gly His Leu Val Pro Ala Ser Trp Lys Leu
610 615 620

Gln Val Val Lys Gln Leu Ala Tyr Ala Leu Asn Tyr Leu Glu Asp Lys
625 630 635 640

Gly Leu Ser His Gly Asn Val Ser Ala Arg Lys Val Leu Leu Ala Arg
645 650 655

Glu Gly Ala Asp Gly Ser Pro Pro Phe Ile Lys Leu Ser Asp Pro Gly
660 665 670

Val Ser Pro Ala Val Leu Ser Leu Glu Met Leu Thr Asp Arg Ile Pro
675 680 685

Trp Val Ala Pro Glu Cys Leu Arg Glu Ala Gln Thr Leu Ser Leu Glu
690 695 700

```
Ala Asp Lys Trp Gly Phe Gly Ala Thr Val Trp Glu Val Phe Ser Gly
705                 710                 715                 720

Val Thr Met Pro Ile Ser Ala Leu Asp Pro Ala Lys Lys Leu Gln Phe
                725                 730                 735

Tyr Glu Asp Arg Gln Gln Leu Ser Ala Pro Lys Trp Thr Glu Leu Ala
            740                 745                 750

Leu Leu Ile Gln Gln Cys Met Ala Tyr Glu Pro Val Gln Arg Pro Ser
        755                 760                 765

Leu Arg Ala Val Ile Arg Asp Leu Asn Ser Leu Ile Ser Ser Asp Tyr
    770                 775                 780

Glu Leu Leu Ser Asp His Thr Trp Cys Pro Gly Thr Arg Asp Gly Leu
785                 790                 795                 800

Trp Asn Gly Ala Gln Leu Tyr Ala Cys Gln Asp Pro Thr Ile Phe Glu
                805                 810                 815

Glu Arg His Leu Lys Tyr Ile Ser Gln Leu Gly Lys Gly Phe Phe Gly
            820                 825                 830

Ser Val Glu Leu Cys Arg Tyr Asp Pro Leu Gly Asp Asn Thr Gly Ala
        835                 840                 845

Leu Val Ala Val Lys Gln Leu Gln His Ser Gly Pro Asp Gln Gln Arg
    850                 855                 860

Asp Phe Gln Arg Glu Ile Gln Ile Leu Lys Ala Gln His Ser Asp Phe
865                 870                 875                 880

Ile Val Lys Tyr Arg Gly Val Ser Tyr Gly Pro Gly Arg Gln Ser Pro
                885                 890                 895

Ala Leu Val Met Glu Tyr Leu Pro Ser Gly Cys Leu Arg Asp Phe Leu
            900                 905                 910

Gln Arg His Arg Gly Leu Asp Ala Ser Arg Leu Leu Leu Tyr Ser Ser
        915                 920                 925

Gln Ile Cys Lys Gly Met Glu Tyr Leu Gly Ser Arg Arg Cys Val His
    930                 935                 940

Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Glu Ser Glu Ala His Val
945                 950                 955                 960

Lys Ile Ala Asp Phe Gly Leu Ala Lys Leu Leu Pro Leu Asp Lys Asp
                965                 970                 975

Tyr Tyr Val Val Arg Glu Pro Gly Gln Ser Pro Ile Phe Trp Tyr Ala
            980                 985                 990

Pro Glu Ser Leu Ser Asp Asn Ile Phe Ser Arg Gln Ser Asp Val Trp
        995                 1000                1005

Ser Phe Gly Val Val Leu Tyr Glu Leu Phe Thr Tyr Cys Asp Lys Ser
    1010                1015                1020

Cys Ser Pro Ser Ala Glu Phe Leu Arg Met Met Gly Cys Glu Arg Asp
1025                1030                1035                1040

Val Pro Arg Leu Cys Arg Leu Leu Glu Leu Leu Glu Glu Gly Gln Arg
                1045                1050                1055

Leu Pro Ala Pro Pro Cys Cys Pro
            1060
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AGCCGCCTCC TTCTCT 16

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CGGCAGCAGC TTAGCTAGG 19

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1082 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Met Ala Pro Pro Ser Glu Glu Thr Pro Leu Ile Pro Gln Arg Ser Cys
1               5                   10                  15

Ser Leu Leu Ser Thr Glu Ala Gly Ala Leu His Val Leu Leu Pro Ala
            20                  25                  30

Arg Gly Pro Gly Pro Pro Gln Arg Leu Ser Phe Ser Phe Gly Asp His
        35                  40                  45

Leu Ala Glu Asp Leu Cys Val Gln Ala Ala Lys Ala Ser Ala Ile Leu
    50                  55                  60

Pro Val Tyr His Ser Leu Phe Ala Leu Ala Thr Glu Asp Leu Ser Cys
65                  70                  75                  80

Trp Phe Pro Arg Ala Thr Ser Ser Pro Trp Arg Met Pro Ala Pro Gln
                85                  90                  95

Val Leu Leu Tyr Arg Ile Arg Phe Tyr Phe Pro Asn Trp Phe Gly Leu
            100                 105                 110
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Glu Lys Cys His Arg Phe Gly Leu Arg Lys Asp Leu Ala Ser Ala Ile
        115                 120                 125

Leu Asp Leu Pro Val Leu Glu His Leu Phe Ala Gln His Arg Ser Asp
    130                 135                 140

Leu Val Ser Gly Arg Leu Pro Arg Gly Leu Ser Leu Lys Glu Gln Gly
145                 150                 155                 160

Glu Cys Leu Ser Leu Ala Val Leu Asp Leu Ala Arg Met Ala Arg Glu
                165                 170                 175

Gln Ala Gln Arg Arg Gly Glu Leu Leu Lys Thr Val Ser Tyr Lys Ala
            180                 185                 190

Cys Leu Pro Pro Ser Leu Arg Asp Leu Ile Gln Gly Leu Ser Phe Val
        195                 200                 205

Thr Gly Arg Arg Ile Arg Arg Thr Val Glu Ser Pro Leu Arg Arg Val
    210                 215                 220

Ala Ala Cys Gln Ala Asp Arg His Ser Leu Met Ala Lys Tyr Ile Met
225                 230                 235                 240

Asp Leu Glu Arg Leu Asp Pro Ala Gly Ala Ala Glu Thr Phe His Val
                245                 250                 255

Gly Leu Pro Gly Ala Leu Gly Gly His Asp Gly Leu Gly Leu Val Arg
            260                 265                 270

Val Ala Gly Asp Gly Gly Ile Ala Trp Thr Gln Gly Glu Gln Glu Val
        275                 280                 285

Leu Gln Pro Phe Cys Asp Phe Pro Glu Ile Val Asp Ile Ser Ile Lys
    290                 295                 300

Gln Ala Pro Arg Val Gly Pro Ala Gly Glu His Arg Leu Val Thr Val
305                 310                 315                 320

Thr Arg Thr Asp Asn Gln Ile Leu Glu Ala Glu Phe Pro Gly Leu Pro
                325                 330                 335

Glu Ala Leu Ser Phe Val Ala Leu Val Asp Gly Tyr Phe Arg Leu Thr
            340                 345                 350

Thr Asp Ser Gln His Phe Phe Cys Lys Glu Val Asp Pro Arg Leu Leu
        355                 360                 365

Glu Glu Val Ala Glu Gln Cys His Gly Pro Ile Thr Leu Asp Phe Ala
    370                 375                 380

Ile Asn Lys Leu Lys Thr Gly Gly Ser Arg Pro Gly Ser Tyr Val Leu
385                 390                 395                 400

Arg Arg Ile Pro Gln Asp Phe Asp Ser Phe Leu Leu Thr Val Cys Val
                405                 410                 415

Gln Asn Pro Leu Gly Pro Asp Tyr Lys Gly Cys Leu Ile Arg Arg Ser
            420                 425                 430

Pro Thr Gly Thr Phe Leu Leu Val Gly Leu Ser Arg Pro His Ser Ser
        435                 440                 445

Leu Arg Glu Leu Leu Ala Thr Cys Trp Asp Gly Gly Leu His Val Asp
    450                 455                 460

Gly Val Ala Val Thr Leu Thr Ser Cys Cys Ile Pro Arg Pro Lys Glu
465                 470                 475                 480

Lys Ser Asn Leu Ile Val Val Gln Arg Gly His Ser Pro Pro Thr Ser
                485                 490                 495
```

Ser Leu Val Gln Pro Gln Ser Gln Tyr Gln Leu Ser Gln Met Thr Phe
500 505 510

His Lys Ile Pro Ala Asp Ser Leu Glu Trp His Glu Asn Leu Gly His
515 520 525

Gly Ser Phe Thr Lys Ile Tyr Arg Gly Cys Arg His Glu Val Val Asp
530 535 540

Gly Glu Ala Arg Lys Thr Glu Val Leu Leu Lys Val Met Asp Ala Lys
545 550 555 560

His Lys Asn Cys Met Glu Ser Phe Leu Glu Ala Ala Ser Leu Met Ser
565 570 575

Gln Val Ser Tyr Arg His Leu Val Leu Leu His Gly Val Cys Met Ala
580 585 590

Gly Asp Ser Thr Met Val Glu Glu Phe Val His Leu Gly Ala Ile Asp
595 600 605

Met Tyr Leu Arg Lys Arg Gly His Leu Val Pro Ala Ser Trp Lys Leu
610 615 620

Gln Val Val Lys Gln Leu Ala Tyr Ala Leu Asn Tyr Leu Glu Asp Lys
625 630 635 640

Gly Leu Ser His Gly Asn Val Ser Ala Arg Lys Val Leu Leu Ala Arg
645 650 655

Glu Gly Ala Asp Gly Ser Pro Pro Phe Ile Lys Leu Ser Asp Pro Gly
660 665 670

Val Ser Pro Ala Val Leu Ser Leu Glu Met Leu Thr Asp Arg Ile Pro
675 680 685

Trp Val Ala Pro Glu Cys Leu Arg Glu Ala Gln Thr Leu Ser Leu Glu
690 695 700

Ala Asp Lys Trp Gly Phe Gly Ala Thr Val Trp Glu Val Phe Ser Gly
705 710 715 720

Val Thr Met Pro Ile Ser Ala Leu Asp Pro Ala Lys Lys Leu Gln Phe
725 730 735

Tyr Glu Asp Arg Gln Gln Leu Ser Ala Pro Lys Trp Thr Glu Leu Ala
740 745 750

Leu Leu Ile Gln Gln Cys Met Ala Tyr Glu Pro Val Gln Arg Pro Ser
755 760 765

Leu Arg Ala Val Ile Arg Asp Leu Asn Ser Leu Ile Ser Ser Asp Tyr
770 775 780

Glu Leu Leu Ser Asp His Thr Trp Cys Pro Gly Thr Arg Asp Gly Leu
785 790 795 800

Trp Asn Gly Ala Gln Leu Tyr Ala Cys Gln Asp Pro Thr Ile Phe Glu
805 810 815

Glu Arg His Leu Lys Tyr Ile Ser Gln Leu Gly Lys Gly Phe Phe Gly
820 825 830

Ser Val Glu Leu Cys Arg Tyr Asp Pro Leu Gly Asp Asn Thr Gly Ala
835 840 845

Leu Val Ala Val Lys Gln Leu Gln His Ser Gly Pro Asp Gln Gln Arg
850 855 860

Asp Phe Gln Arg Glu Ile Gln Ile Leu Lys Ala Gln His Ser Asp Phe
865 870 875 880

```
Ile Val Lys Tyr Arg Gly Val Ser Tyr Gly Pro Gly Arg Gln Ser Pro
                885                 890                 895

Ala Leu Val Met Glu Tyr Leu Pro Ser Gly Cys Leu Arg Asp Phe Leu
            900                 905                 910

Gln Arg His Arg Gly Leu Asp Ala Ser Arg Leu Leu Leu Tyr Ser Ser
        915                 920                 925

Gln Ile Cys Lys Gly Met Glu Tyr Leu Gly Ser Arg Arg Cys Val His
    930                 935                 940

Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Glu Ser Glu Ala His Val
945                 950                 955                 960

Lys Ile Ala Asp Phe Gly Leu Ala Lys Leu Leu Pro Leu Asp Lys Asp
                965                 970                 975

Tyr Tyr Val Val Arg Glu Pro Gly Gln Ser Pro Ile Phe Trp Tyr Ala
            980                 985                 990

Pro Glu Ser Leu Ser Asp Asn Ile Phe Ser Arg Gln Ser Asp Val Trp
        995                1000                1005

Ser Phe Gly Val Val Leu Tyr Glu Leu Phe Thr Tyr Cys Asp Lys Ser
    1010                1015                1020

Cys Ser Pro Ser Ala Glu Phe Leu Arg Met Met Gly Cys Glu Arg Asp
1025                1030                1035                1040

Val Pro Arg Leu Cys Arg Leu Leu Glu Leu Leu Glu Glu Gly Gln Arg
                1045                1050                1055

Leu Pro Ala Pro Pro Cys Cys Pro Ala Glu Val Ser Cys Tyr Ser Gly
            1060                1065                1070

Trp Arg Asp Asp Ile Cys Leu Pro Ala Glu
        1075                1080
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1129 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Met Gly Met Ala Cys Leu Thr Met Thr Glu Met Glu Ala Thr Ser Thr
1               5                   10                  15

Ser Pro Val His Gln Asn Gly Asp Ile Pro Gly Ser Ala Asn Ser Val
            20                  25                  30

Lys Gln Ile Glu Pro Val Leu Gln Val Tyr Leu Tyr His Ser Leu Gly
        35                  40                  45

Gln Ala Glu Gly Glu Tyr Leu Lys Phe Pro Ser Gly Glu Tyr Val Ala
    50                  55                  60

Glu Glu Ile Cys Val Ala Ala Ser Lys Ala Cys Gly Ile Thr Pro Val
65                  70                  75                  80

Tyr His Asn Met Phe Ala Leu Met Ser Glu Thr Glu Arg Ile Trp Tyr
                85                  90                  95
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Pro Pro Asn His Val Phe His Ile Asp Glu Ser Thr Arg His Asp Ile
            100                 105                 110

Leu Tyr Arg Ile Arg Phe Tyr Phe Pro His Trp Tyr Cys Ser Gly Ser
        115                 120                 125

Ser Arg Thr Tyr Arg Tyr Gly Val Ser Arg Gly Ala Glu Ala Pro Leu
    130                 135                 140

Leu Asp Asp Phe Val Met Ser Tyr Leu Phe Val Gln Trp Arg His Asp
145                 150                 155                 160

Phe Val His Gly Trp Ile Lys Val Pro Val Thr His Glu Thr Gln Glu
                165                 170                 175

Glu Cys Leu Gly Met Ala Val Leu Asp Met Met Arg Ile Ala Lys Glu
            180                 185                 190

Lys Asp Gln Thr Pro Leu Ala Val Tyr Asn Ser Val Ser Tyr Lys Thr
        195                 200                 205

Phe Leu Pro Lys Cys Val Arg Ala Lys Ile Gln Asp Tyr His Ile Leu
    210                 215                 220

Thr Arg Lys Arg Ile Arg Tyr Arg Phe Arg Arg Phe Ile Gln Gln Phe
225                 230                 235                 240

Ser Gln Cys Lys Ala Thr Ala Arg Asn Leu Lys Leu Lys Tyr Leu Ile
                245                 250                 255

Asn Leu Glu Thr Leu Gln Ser Ala Phe Tyr Thr Glu Gln Phe Glu Val
            260                 265                 270

Lys Glu Ser Ala Arg Gly Pro Ser Gly Glu Glu Ile Phe Ala Thr Ile
        275                 280                 285

Ile Ile Thr Gly Asn Gly Gly Ile Gln Trp Ser Arg Gly Lys His Lys
    290                 295                 300

Glu Ser Glu Thr Leu Thr Glu Gln Asp Val Gln Leu Tyr Cys Asp Phe
305                 310                 315                 320

Pro Asp Ile Ile Asp Val Ser Ile Lys Gln Ala Asn Gln Glu Cys Ser
                325                 330                 335

Asn Glu Ser Arg Ile Val Thr Val His Lys Gln Asp Gly Lys Val Leu
            340                 345                 350

Glu Ile Glu Leu Ser Ser Leu Lys Glu Ala Leu Ser Phe Val Ser Leu
        355                 360                 365

Ile Asp Gly Tyr Tyr Arg Leu Thr Ala Asp Ala His His Tyr Leu Cys
    370                 375                 380

Lys Glu Val Ala Pro Pro Ala Val Leu Glu Asn Ile His Ser Asn Cys
385                 390                 395                 400

His Gly Pro Ile Ser Met Asp Phe Ala Ile Ser Lys Leu Lys Lys Ala
                405                 410                 415

Gly Asn Gln Thr Gly Leu Tyr Val Leu Arg Cys Ser Pro Lys Asp Phe
            420                 425                 430

Asn Lys Tyr Phe Leu Thr Phe Ala Val Glu Arg Glu Asn Val Ile Glu
        435                 440                 445

Tyr Lys His Cys Leu Ile Thr Lys Asn Glu Asn Gly Glu Tyr Asn Leu
    450                 455                 460

Ser Gly Thr Asn Arg Asn Phe Ser Asn Leu Lys Asp Leu Leu Asn Cys
465                 470                 475                 480
```

```
Tyr Gln Met Glu Thr Val Arg Ser Asp Ser Ile Ile Phe Gln Phe Thr
                485                 490                 495

Lys Cys Cys Pro Pro Lys Pro Lys Asp Lys Ser Asn Leu Leu Val Phe
            500                 505                 510

Arg Thr Asn Gly Ile Ser Asp Val Gln Ile Ser Pro Thr Leu Gln Arg
        515                 520                 525

His Asn Asn Val Asn Gln Met Val Phe His Lys Ile Arg Asn Glu Asp
    530                 535                 540

Leu Ile Phe Asn Glu Ser Leu Gly Gln Gly Thr Phe Thr Lys Ile Phe
545                 550                 555                 560

Lys Gly Val Arg Arg Glu Val Gly Asp Tyr Gly Gln Leu His Lys Thr
                565                 570                 575

Glu Val Leu Leu Lys Val Leu Asp Lys Ala His Arg Asn Tyr Ser Glu
            580                 585                 590

Ser Phe Phe Glu Ala Ala Ser Met Met Ser Gln Leu Ser His Lys His
        595                 600                 605

Leu Val Leu Asn Tyr Gly Val Cys Val Cys Gly Glu Glu Asn Ile Leu
    610                 615                 620

Val Gln Glu Phe Val Lys Phe Gly Ser Leu Asp Thr Tyr Leu Lys Lys
625                 630                 635                 640

Asn Lys Asn Ser Ile Asn Ile Leu Trp Lys Leu Gly Val Ala Lys Gln
                645                 650                 655

Leu Ala Trp Ala Met His Phe Leu Glu Glu Lys Ser Leu Ile His Gly
            660                 665                 670

Asn Val Cys Ala Lys Asn Ile Leu Leu Ile Arg Glu Glu Asp Arg Arg
        675                 680                 685

Thr Gly Asn Pro Pro Phe Ile Lys Leu Ser Asp Pro Gly Ile Ser Ile
    690                 695                 700

Thr Val Leu Pro Lys Asp Ile Leu Gln Glu Arg Ile Pro Trp Val Pro
705                 710                 715                 720

Pro Glu Cys Ile Glu Asn Pro Lys Asn Leu Asn Leu Ala Thr Asp Lys
                725                 730                 735

Trp Ser Phe Gly Thr Thr Leu Trp Glu Ile Cys Ser Gly Gly Asp Lys
            740                 745                 750

Pro Leu Ser Ala Leu Asp Ser Gln Arg Lys Leu Gln Phe Tyr Glu Asp
        755                 760                 765

Lys His Gln Leu Pro Ala Pro Lys Trp Thr Glu Leu Ala Asn Leu Ile
    770                 775                 780

Asn Asn Cys Met Asp Tyr Glu Pro Asp Phe Arg Pro Ala Phe Arg Ala
785                 790                 795                 800

Val Ile Arg Asp Leu Asn Ser Leu Phe Thr Pro Asp Tyr Glu Leu Leu
                805                 810                 815

Thr Glu Asn Asp Met Leu Pro Asn Met Arg Ile Gly Ala Leu Gly Phe
            820                 825                 830

Ser Gly Ala Phe Glu Asp Arg Asp Pro Thr Gln Phe Glu Glu Arg His
        835                 840                 845

Leu Lys Phe Leu Gln Gln Leu Gly Lys Gly Asn Phe Gly Ser Val Glu
    850                 855                 860
```

```
Met Cys Arg Tyr Asp Pro Leu Gln Asp Asn Thr Gly Glu Val Val Ala
865                 870                 875                 880

Val Lys Lys Leu Gln His Ser Thr Glu Glu His Leu Arg Asp Phe Glu
                885                 890                 895

Arg Glu Ile Glu Ile Leu Lys Ser Leu Gln His Asp Asn Ile Val Lys
            900                 905                 910

Tyr Lys Gly Val Cys Tyr Ser Ala Gly Arg Arg Asn Leu Arg Leu Ile
        915                 920                 925

Met Glu Tyr Leu Pro Tyr Gly Ser Leu Arg Asp Tyr Leu Gln Lys His
    930                 935                 940

Lys Glu Arg Ile Asp His Lys Lys Leu Leu Gln Tyr Thr Ser Gln Ile
945                 950                 955                 960

Cys Lys Gly Met Glu Tyr Leu Gly Thr Lys Arg Tyr Ile His Arg Asp
                965                 970                 975

Leu Ala Thr Arg Asn Ile Leu Val Glu Asn Glu Asn Arg Val Lys Ile
            980                 985                 990

Gly Asp Phe Gly Leu Thr Lys Val Leu Pro Gln Asp Lys Glu Tyr Tyr
        995                 1000                1005

Lys Val Lys Glu Pro Gly Glu Ser Pro Ile Phe Trp Tyr Ala Pro Gln
    1010                1015                1020

Ser Leu Thr Glu Ser Lys Phe Ser Val Ala Ser Asp Val Trp Ser Phe
1025                1030                1035                1040

Gly Val Val Leu Tyr Glu Leu Phe Thr Tyr Ile Glu Lys Ser Lys Ser
                1045                1050                1055

Pro Pro Val Glu Phe Met Arg Met Ile Gly Asn Asp Lys Gln Gly Gln
            1060                1065                1070

Met Ile Val Phe His Leu Ile Glu Leu Leu Lys Ser Asn Gly Arg Leu
        1075                1080                1085

Pro Arg Pro Glu Gly Cys Pro Asp Glu Ile Tyr Val Ile Met Thr Glu
    1090                1095                1100

Cys Trp Asn Asn Asn Val Ser Gln Arg Pro Ser Phe Arg Asp Leu Ser
1105                1110                1115                1120

Phe Gly Trp Ile Lys Cys Gly Thr Val
                1125
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1154 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Met Gln Tyr Leu Asn Ile Lys Glu Asp Cys Asn Ala Met Ala Phe Cys
1               5                   10                  15

Ala Lys Met Arg Ser Ser Lys Lys Thr Glu Val Asn Leu Glu Ala Pro
            20                  25                  30
```

```
Glu Pro Gly Val Glu Val Ile Phe Tyr Leu Ser Asp Arg Glu Pro Leu
        35                  40                  45

Arg Leu Gly Ser Gly Glu Tyr Thr Ala Glu Glu Leu Cys Ile Arg Ala
    50                  55                  60

Ala Gln Ala Cys Arg Ile Ser Pro Leu Cys His Asn Leu Phe Ala Leu
65                  70                  75                  80

Tyr Asp Glu Asn Thr Lys Leu Trp Tyr Ala Pro Asn Arg Thr Ile Thr
                85                  90                  95

Val Asp Asp Lys Met Ser Leu Arg Leu His Tyr Arg Met Arg Phe Tyr
            100                 105                 110

Phe Thr Asn Trp His Gly Thr Asn Asp Asn Glu Gln Ser Val Trp Arg
        115                 120                 125

His Ser Pro Lys Lys Gln Lys Asn Gly Tyr Glu Lys Lys Lys Ile Pro
    130                 135                 140

Asp Ala Thr Pro Leu Leu Asp Ala Ser Ser Leu Glu Tyr Leu Phe Ala
145                 150                 155                 160

Gln Gly Gln Tyr Asp Leu Val Lys Cys Leu Ala Pro Ile Arg Asp Pro
                165                 170                 175

Lys Thr Glu Gln Asp Gly His Asp Ile Glu Asn Glu Cys Leu Gly Met
            180                 185                 190

Ala Val Leu Ala Ile Ser His Tyr Ala Met Met Lys Lys Met Gln Leu
        195                 200                 205

Pro Glu Leu Pro Lys Asp Ile Ser Tyr Lys Arg Tyr Ile Pro Glu Thr
    210                 215                 220

Leu Asn Lys Ser Ile Arg Gln Arg Asn Leu Leu Thr Arg Met Arg Ile
225                 230                 235                 240

Asn Asn Val Phe Lys Asp Phe Leu Lys Glu Phe Asn Asn Lys Thr Ile
                245                 250                 255

Cys Asp Ser Ser Val Ser Thr His Asp Leu Lys Val Lys Tyr Leu Ala
            260                 265                 270

Thr Leu Glu Thr Leu Thr Lys His Tyr Gly Ala Glu Ile Phe Glu Thr
        275                 280                 285

Ser Met Leu Leu Ile Ser Ser Glu Asn Glu Met Asn Trp Phe His Ser
    290                 295                 300

Asn Asp Gly Gly Asn Val Leu Tyr Tyr Glu Val Met Val Thr Gly Asn
305                 310                 315                 320

Leu Gly Ile Gln Trp Arg His Lys Pro Asn Val Val Ser Val Glu Lys
                325                 330                 335

Glu Lys Asn Lys Leu Lys Arg Lys Lys Leu Glu Asn Lys Asp Lys Lys
            340                 345                 350

Asp Glu Glu Lys Asn Lys Ile Arg Glu Glu Trp Asn Asn Phe Ser Phe
        355                 360                 365

Phe Pro Glu Ile Thr His Ile Val Ile Lys Glu Ser Val Val Ser Ile
    370                 375                 380

Asn Lys Gln Asp Asn Lys Lys Met Glu Leu Lys Leu Ser Ser His Glu
385                 390                 395                 400

Glu Ala Leu Ser Phe Val Ser Leu Val Asp Gly Tyr Phe Arg Leu Thr
                405                 410                 415
```

Ala Asp Ala His His Tyr Leu Cys Thr Asp Val Ala Pro Pro Leu Ile
420 425 430

Val His Asn Ile Gln Asn Gly Cys His Gly Pro Ile Cys Thr Glu Tyr
435 440 445

Ala Ile Asn Lys Leu Arg Gln Glu Gly Ser Glu Glu Gly Met Tyr Val
450 455 460

Leu Arg Trp Ser Cys Thr Asp Phe Asp Asn Ile Leu Met Thr Val Thr
465 470 475 480

Cys Phe Glu Lys Ser Glu Gln Val Gln Gly Ala Gln Lys Gln Phe Lys
485 490 495

Asn Phe Gln Ile Glu Val Gln Lys Gly Arg Tyr Ser Leu His Gly Ser
500 505 510

Asp Arg Ser Phe Pro Ser Leu Gly Asp Leu Met Ser His Leu Lys Lys
515 520 525

Gln Ile Leu Arg Thr Asp Asn Ile Ser Phe Met Leu Lys Arg Cys Cys
530 535 540

Gln Pro Lys Pro Arg Glu Ile Ser Asn Leu Leu Val Ala Thr Lys Lys
545 550 555 560

Ala Gln Glu Trp Gln Pro Val Tyr Pro Met Ser Gln Leu Ser Phe Asp
565 570 575

Arg Ile Leu Lys Lys Asp Leu Val Gln Gly Glu His Leu Gly Arg Gly
580 585 590

Thr Arg Thr His Ile Tyr Ser Gly Thr Leu Met Asp Tyr Lys Asp Asp
595 600 605

Glu Gly Thr Ser Glu Glu Lys Lys Ile Lys Val Ile Leu Lys Val Leu
610 615 620

Asp Pro Ser His Arg Asp Ile Ser Leu Ala Phe Phe Glu Ala Ala Ser
625 630 635 640

Met Met Arg Gln Val Ser His Lys His Ile Val Tyr Leu Tyr Gly Val
645 650 655

Cys Val Arg Asp Val Glu Asn Ile Met Val Glu Glu Phe Val Glu Gly
660 665 670

Gly Pro Leu Asp Leu Phe Met His Arg Lys Ser Asp Val Leu Thr Thr
675 680 685

Pro Trp Lys Phe Lys Val Ala Lys Gln Leu Ala Ser Ala Leu Ser Tyr
690 695 700

Leu Glu Asp Lys Asp Leu Val His Gly Asn Val Cys Thr Lys Asn Leu
705 710 715 720

Leu Leu Ala Arg Glu Gly Ile Asp Ser Glu Cys Gly Pro Phe Ile Lys
725 730 735

Leu Ser Asp Pro Gly Ile Pro Ile Thr Val Leu Ser Arg Gln Glu Cys
740 745 750

Ile Glu Arg Ile Pro Trp Ile Ala Pro Glu Cys Val Glu Asp Ser Lys
755 760 765

Asn Leu Ser Val Ala Ala Asp Lys Trp Ser Phe Gly Thr Thr Leu Trp
770 775 780

Glu Ile Cys Tyr Asn Gly Glu Ile Pro Leu Lys Asp Lys Thr Leu Ile
785 790 795 800

Glu Lys Glu Arg Phe Tyr Glu Ser Arg Cys Arg Pro Val Thr Pro Ser
805 810 815

Cys Lys Glu Leu Ala Asp Leu Met Thr Arg Cys Met Asn Tyr Asp Pro
820 825 830

Asn Gln Arg Pro Phe Phe Arg Ala Ile Met Arg Asp Ile Asn Lys Leu
835 840 845

Glu Glu Gln Asn Pro Asp Ile Val Ser Arg Lys Lys Asn Gln Pro Thr
850 855 860

Glu Val Asp Pro Thr His Phe Glu Lys Arg Phe Leu Lys Arg Ile Arg
865 870 875 880

Asp Leu Gly Glu Gly His Phe Gly Lys Val Glu Leu Cys Arg Tyr Asp
885 890 895

Pro Glu Asp Asn Thr Gly Glu Gln Val Ala Val Lys Ser Leu Lys Pro
900 905 910

Glu Ser Gly Gly Asn His Ile Ala Asp Leu Lys Lys Glu Ile Glu Ile
915 920 925

Leu Arg Asn Leu Tyr His Glu Asn Ile Val Lys Tyr Lys Gly Ile Cys
930 935 940

Thr Glu Asp Gly Gly Asn Gly Ile Lys Leu Ile Met Glu Phe Leu Pro
945 950 955 960

Ser Gly Ser Leu Lys Glu Tyr Leu Pro Lys Asn Lys Asn Lys Ile Asn
965 970 975

Leu Lys Gln Gln Leu Lys Tyr Ala Val Gln Ile Cys Lys Gly Met Asp
980 985 990

Tyr Leu Gly Ser Arg Gln Tyr Val His Arg Asp Leu Ala Ala Arg Asn
995 1000 1005

Val Leu Val Glu Ser Glu His Gln Val Lys Ile Gly Asp Phe Gly Leu
1010 1015 1020

Thr Lys Ala Ile Glu Thr Asp Lys Glu Tyr Tyr Thr Val Lys Asp Asp
1025 1030 1035 1040

Arg Asp Ser Pro Val Phe Trp Tyr Ala Pro Glu Cys Leu Met Gln Ser
1045 1050 1055

Lys Phe Tyr Ile Ala Ser Asp Val Trp Ser Phe Gly Val Thr Leu His
1060 1065 1070

Glu Leu Leu Thr Tyr Cys Asp Ser Asp Ser Ser Pro Met Ala Leu Phe
1075 1080 1085

Leu Lys Met Ile Gly Pro Thr His Gly Gln Met Thr Val Thr Arg Leu
1090 1095 1100

Val Asn Thr Leu Lys Glu Gly Lys Arg Leu Pro Cys Pro Pro Asn Cys
1105 1110 1115 1120

Pro Asp Glu Val Tyr Gln Leu Met Arg Lys Cys Trp Glu Phe Gln Pro
1125 1130 1135

Ser Asn Arg Thr Ser Phe Gln Asn Leu Ile Glu Gly Phe Glu Ala Leu
1140 1145 1150

Leu Lys

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1187 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Met Pro Leu Arg His Trp Gly Met Ala Arg Gly Ser Lys Pro Val Gly
1               5                   10                  15

Asp Gly Ala Gln Pro Met Ala Ala Met Gly Gly Leu Lys Val Leu Leu
            20                  25                  30

His Trp Ala Gly Pro Gly Gly Gly Glu Pro Trp Val Thr Phe Ser Glu
        35                  40                  45

Ser Ser Leu Thr Ala Glu Glu Val Cys Ile His Ile Ala His Lys Val
    50                  55                  60

Gly Ile Thr Pro Pro Cys Phe Asn Leu Phe Ala Leu Phe Asp Ala Gln
65                  70                  75                  80

Ala Gln Val Trp Leu Pro Pro Asn His Ile Leu Glu Ile Pro Arg Asp
                85                  90                  95

Ala Ser Leu Met Leu Tyr Phe Arg Ile Arg Phe Tyr Phe Arg Asn Trp
            100                 105                 110

His Gly Met Asn Pro Arg Glu Pro Ala Val Tyr Arg Cys Gly Pro Pro
        115                 120                 125

Gly Thr Glu Ala Ser Ser Asp Gln Thr Ala Gln Gly Met Gln Leu Leu
    130                 135                 140

Asp Pro Ala Ser Phe Glu Tyr Leu Phe Glu Gln Gly Lys His Glu Phe
145                 150                 155                 160

Val Asn Asp Val Ala Ser Leu Trp Glu Leu Ser Thr Glu Glu Glu Ile
                165                 170                 175

His His Phe Lys Asn Glu Ser Leu Gly Met Ala Phe Leu His Leu Cys
            180                 185                 190

His Leu Ala Leu Arg His Gly Ile Pro Leu Glu Glu Val Ala Lys Lys
        195                 200                 205

Thr Ser Phe Lys Asp Cys Ile Pro Arg Ser Phe Arg Arg His Ile Arg
    210                 215                 220

Gln His Ser Ala Leu Thr Arg Leu Arg Leu Arg Asn Val Phe Arg Arg
225                 230                 235                 240

Phe Leu Arg Asp Phe Gln Pro Gly Arg Leu Ser Gln Gln Met Val Met
                245                 250                 255

Val Lys Tyr Leu Ala Thr Leu Glu Arg Leu Ala Pro Arg Phe Gly Thr
            260                 265                 270

Glu Arg Val Pro Val Cys His Leu Arg Leu Leu Ala Gln Ala Glu Gly
        275                 280                 285

Glu Pro Cys Tyr Ile Arg Asp Ser Gly Val Ala Pro Thr Asp Pro Gly
    290                 295                 300
```

Pro Glu Ser Ala Ala Gly Pro Pro Thr His Glu Val Leu Val Thr Gly
305 310 315 320

Thr Gly Gly Ile Gln Trp Trp Pro Val Glu Glu Glu Val Asn Lys Glu
325 330 335

Glu Gly Ser Ser Gly Ser Ser Gly Arg Asn Pro Gln Ala Ser Leu Phe
340 345 350

Gly Lys Lys Ala Lys Ala His Lys Ala Phe Gly Gln Pro Ala Asp Arg
355 360 365

Pro Arg Glu Pro Leu Trp Ala Tyr Phe Cys Asp Phe Arg Asp Ile Thr
370 375 380

His Val Val Leu Lys Glu His Cys Val Ser Ile His Arg Gln Asp Asn
385 390 395 400

Lys Cys Leu Glu Leu Ser Leu Pro Ser Arg Ala Ala Ala Leu Ser Phe
405 410 415

Val Ser Leu Val Asp Gly Tyr Phe Arg Leu Thr Ala Asp Ser Ser His
420 425 430

Tyr Leu Cys His Glu Val Ala Pro Pro Arg Leu Val Met Ser Ile Arg
435 440 445

Asp Gly Ile His Gly Pro Leu Leu Glu Pro Phe Val Gln Ala Lys Leu
450 455 460

Arg Pro Glu Asp Gly Leu Tyr Leu Ile His Trp Ser Thr Ser His Pro
465 470 475 480

Tyr Arg Leu Ile Leu Thr Val Ala Gln Arg Ser Gln Ala Pro Asp Gly
485 490 495

Met Gln Ser Leu Arg Leu Arg Lys Phe Pro Ile Glu Gln Gln Asp Gly
500 505 510

Ala Phe Val Leu Glu Gly Trp Gly Arg Ser Phe Pro Ser Val Arg Glu
515 520 525

Leu Gly Ala Ala Leu Gln Gly Cys Leu Leu Arg Ala Gly Asp Asp Cys
530 535 540

Phe Ser Leu Arg Arg Cys Cys Leu Pro Gln Pro Gly Glu Thr Ser Asn
545 550 555 560

Leu Ile Ile Met Arg Gly Ala Arg Ala Ser Pro Arg Thr Leu Asn Leu
565 570 575

Ser Gln Leu Ser Phe His Arg Val Asp Gln Lys Glu Ile Thr Gln Leu
580 585 590

Ser His Leu Gly Gln Gly Thr Arg Thr Asn Val Tyr Glu Gly Arg Leu
595 600 605

Arg Val Glu Gly Ser Gly Asp Pro Glu Glu Gly Lys Met Asp Asp Glu
610 615 620

Asp Pro Leu Val Pro Gly Arg Asp Arg Gly Gln Glu Leu Arg Val Val
625 630 635 640

Leu Lys Val Leu Asp Pro Ser His His Asp Ile Ala Leu Ala Phe Tyr
645 650 655

Glu Thr Ala Ser Leu Met Ser Gln Val Ser His Thr His Leu Ala Phe
660 665 670

Val His Gly Val Cys Val Arg Gly Pro Glu Asn Ser Met Val Thr Glu
675 680 685

Tyr Val Glu His Gly Pro Leu Asp Val Trp Leu Arg Arg Glu Arg Gly
690 695 700

His Val Pro Met Ala Trp Lys Met Val Val Ala Gln Gln Leu Ala Ser
705 710 715 720

Ala Leu Ser Tyr Leu Glu Asn Lys Asn Leu Val His Gly Asn Val Cys
725 730 735

Gly Arg Asn Ile Leu Leu Ala Arg Leu Gly Leu Ala Glu Gly Thr Ser
740 745 750

Pro Phe Ile Lys Leu Ser Asp Pro Gly Val Gly Leu Gly Ala Leu Ser
755 760 765

Arg Glu Glu Arg Val Glu Arg Ile Pro Trp Leu Ala Pro Glu Cys Leu
770 775 780

Pro Gly Gly Ala Asn Ser Leu Ser Thr Ala Met Asp Lys Trp Gly Phe
785 790 795 800

Gly Ala Thr Leu Leu Glu Ile Cys Phe Asp Gly Glu Ala Pro Leu Gln
805 810 815

Ser Arg Ser Pro Ser Glu Lys Glu His Phe Tyr Gln Arg Gln His Arg
820 825 830

Leu Pro Glu Pro Ser Cys Pro Gln Leu Ala Thr Leu Thr Ser Gln Cys
835 840 845

Leu Thr Tyr Glu Pro Thr Gln Arg Pro Ser Phe Arg Thr Ile Leu Arg
850 855 860

Asp Leu Thr Arg Val Gln Pro His Asn Leu Ala Asp Val Leu Thr Val
865 870 875 880

Asn Arg Asp Ser Pro Ala Val Gly Pro Thr Thr Phe His Lys Arg Tyr
885 890 895

Leu Lys Lys Ile Arg Asp Leu Gly Glu Gly His Phe Gly Lys Val Ser
900 905 910

Leu Tyr Cys Tyr Asp Pro Thr Asn Asp Gly Thr Gly Glu Met Val Ala
915 920 925

Val Lys Ala Leu Lys Ala Asp Cys Gly Pro Gln His Arg Ser Gly Trp
930 935 940

Lys Gln Glu Ile Asp Ile Leu Arg Thr Leu Tyr His Glu His Ile Ile
945 950 955 960

Lys Tyr Lys Gly Cys Cys Glu Asp Gln Gly Glu Lys Ser Leu Gln Leu
965 970 975

Val Met Glu Tyr Val Pro Leu Gly Ser Leu Arg Asp Tyr Leu Pro Arg
980 985 990

His Ser Ile Gly Leu Ala Gln Leu Leu Leu Phe Ala Gln Gln Ile Cys
995 1000 1005

Glu Gly Met Ala Tyr Leu His Ala His Asp Tyr Ile His Arg Asp Leu
1010 1015 1020

Ala Ala Arg Asn Val Leu Leu Asp Asn Asp Arg Leu Val Lys Ile Gly
1025 1030 1035 1040

Asp Phe Gly Leu Ala Lys Ala Val Pro Glu Gly His Glu Tyr Tyr Arg
1045 1050 1055

Val Arg Glu Asp Gly Asp Ser Pro Val Phe Trp Tyr Ala Pro Glu Cys
1060 1065 1070

```
Leu Lys Glu Tyr Lys Phe Tyr Tyr Ala Ser Asp Val Trp Ser Phe Gly
        1075                1080                1085

Val Thr Leu Tyr Glu Leu Leu Thr His Cys Asp Ser Ser Gln Ser Pro
    1090                1095                1100

Pro Thr Lys Phe Leu Glu Leu Ile Gly Ile Ala Gln Gly Gln Met Thr
1105                1110                1115                1120

Val Leu Arg Leu Thr Glu Leu Leu Glu Arg Gly Glu Arg Leu Pro Arg
                1125                1130                1135

Pro Asp Lys Cys Pro Cys Glu Val Tyr His Leu Met Lys Asn Cys Trp
            1140                1145                1150

Glu Thr Glu Ala Ser Phe Arg Pro Thr Phe Glu Asn Leu Ile Pro Ile
        1155                1160                1165

Leu Lys Thr Val His Glu Lys Tyr Gln Gly Gln Ala Pro Ser Val Phe
    1170                1175                1180

Ser Val Cys
1185
```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 498 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
Met Pro Leu Gly Ala Glu Glu Cys Ala Ala Ile Pro His Asn Leu Phe
1               5                   10                  15

Ala Leu Trp Pro Pro Asn Leu Tyr Arg Ile Arg Phe Tyr Phe Asn Trp
            20                  25                  30

Gly Leu Leu Asp Glu Tyr Leu Phe Gln Asp Val Glu Gln Glu Cys Leu
        35                  40                  45

Gly Met Ala Val Leu Ala Glu Ser Tyr Lys Pro Arg Ile Leu Thr Arg
    50                  55                  60

Arg Ile Arg Phe Phe Leu Phe Leu Lys Lys Tyr Leu Leu Glu Leu Glu
65                  70                  75                  80

Phe Val Val Val Thr Gly Gly Gly Ile Gln Trp Glu Phe Cys Asp Phe
                85                  90                  95

Pro Ile Ile Lys Val Gln Asp Asn Lys Leu Glu Leu Ser Glu Ala Leu
            100                 105                 110

Ser Phe Val Ser Leu Val Asp Gly Tyr Phe Arg Leu Thr Ala Asp His
        115                 120                 125

Tyr Leu Cys Val Ala Pro Pro Ile Cys His Gly Pro Ile Phe Ala Ile
    130                 135                 140

Lys Leu Gly Tyr Val Leu Arg Trp Ser Asp Phe Leu Thr Val Val Lys
145                 150                 155                 160

Ile Gly Leu Gly Arg Phe Ser Leu Arg Phe Cys Cys Pro Pro Ser Asn
                165                 170                 175
```

```
Leu Leu Val Gln Ser Gln Phe His Ile Leu Glu Leu Gly Gly Thr Thr
            180                 185                 190

Ile Tyr Gly Asp Val Leu Lys Val Leu Asp His Phe Glu Ala Ala Ser
        195                 200                 205

Met Ser Gln Val Ser His His Leu Val Gly Val Cys Val Glu Asn Val
    210                 215                 220

Glu Phe Val Gly Leu Asp Arg Trp Lys Val Ala Lys Gln Leu Ala Ala
225                 230                 235                 240

Leu Tyr Leu Glu Asp Leu Leu His Gly Asn Val Cys Asn Ile Leu Leu
                245                 250                 255

Ala Arg Glu Gly Pro Phe Ile Lys Leu Ser Asp Pro Gly Val Leu Ser
            260                 265                 270

Glu Arg Ile Pro Trp Ala Pro Glu Cys Asn Leu Ser Ala Asp Lys Trp
        275                 280                 285

Phe Gly Thr Leu Trp Glu Cys Gly Pro Leu Lys Phe Tyr Glu Leu Pro
    290                 295                 300

Glu Leu Ala Leu Cys Met Tyr Glu Pro Gln Arg Pro Phe Arg Ala Arg
305                 310                 315                 320

Asp Leu Asn Leu Pro Asp Pro Thr Phe Glu Arg Leu Lys Ile Leu Gly
                325                 330                 335

Gly Phe Gly Val Glu Leu Cys Arg Tyr Asp Pro Asp Asn Thr Gly Glu
            340                 345                 350

Val Ala Val Lys Leu Ser Gly His Asp Glu Ile Ile Leu Leu His Ile
        355                 360                 365

Val Lys Tyr Lys Gly Cys Gly Leu Met Glu Tyr Leu Pro Gly Ser Leu
    370                 375                 380

Arg Asp Tyr Leu Ile Leu Leu Leu Tyr Leu Leu Gln Ile Cys Lys Gly
385                 390                 395                 400

Met Tyr Leu Gly Tyr His Arg Asp Leu Ala Ala Arg Asn Leu Val Glu
                405                 410                 415

Glu Val Lys Ile Gly Asp Phe Gly Leu Lys Pro Asp Lys Glu Tyr Tyr
            420                 425                 430

Val Glu Gly Ser Pro Phe Trp Tyr Ala Pro Glu Leu Leu Phe Ala Ser
        435                 440                 445

Asp Val Trp Ser Phe Gly Val Leu Tyr Glu Leu Thr Tyr Cys Asp Ser
    450                 455                 460

Ser Pro Phe Leu Met Ile Gly Gly Gln Met Val Arg Leu Glu Leu Leu
465                 470                 475                 480

Gly Arg Leu Pro Pro Cys Pro Glu Val Tyr Leu Met Cys Trp Ser Arg
                485                 490                 495

Phe Leu
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1082 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met Ala Pro Pro Ser Glu Glu Thr Pro Leu Ile Pro Gln Arg Ser Cys
1 5 10 15

Ser Leu Leu Ser Thr Glu Ala Gly Ala Leu His Val Leu Leu Pro Ala
20 25 30

Arg Gly Pro Gly Pro Pro Gln Arg Leu Ser Phe Ser Phe Gly Asp His
35 40 45

Leu Ala Glu Asp Leu Cys Val Gln Ala Ala Lys Ala Ser Ala Ile Leu
50 55 60

Pro Val Tyr His Ser Leu Phe Ala Leu Ala Thr Glu Asp Leu Ser Cys
65 70 75 80

Trp Phe Pro Arg Ala Thr Ser Ser Pro Trp Arg Met Pro Ala Pro Gln
85 90 95

Val Leu Leu Tyr Arg Ile Arg Phe Tyr Phe Pro Asn Trp Phe Gly Leu
100 105 110

Glu Lys Cys His Arg Phe Gly Leu Arg Lys Asp Leu Ala Ser Ala Ile
115 120 125

Leu Asp Leu Pro Val Leu Glu His Leu Phe Ala Gln His Arg Ser Asp
130 135 140

Leu Val Ser Gly Arg Leu Pro Arg Gly Leu Ser Leu Lys Glu Gln Gly
145 150 155 160

Glu Cys Leu Ser Leu Ala Val Leu Asp Leu Ala Arg Met Ala Arg Glu
165 170 175

Gln Ala Gln Arg Arg Gly Glu Leu Leu Lys Thr Val Ser Tyr Lys Ala
180 185 190

Cys Leu Pro Pro Ser Leu Arg Asp Leu Ile Gln Gly Leu Ser Phe Val
195 200 205

Thr Gly Arg Arg Ile Arg Arg Thr Val Glu Ser Pro Leu Arg Arg Val
210 215 220

Ala Ala Cys Gln Ala Asp Arg His Ser Leu Met Ala Lys Tyr Ile Met
225 230 235 240

Asp Leu Glu Arg Leu Asp Pro Ala Gly Ala Ala Glu Thr Phe His Val
245 250 255

Gly Leu Pro Gly Ala Leu Gly Gly His Asp Gly Leu Gly Leu Val Arg
260 265 270

Val Ala Gly Asp Gly Gly Ile Ala Trp Thr Gln Gly Glu Gln Glu Val
275 280 285

Leu Gln Pro Phe Cys Asp Phe Pro Glu Ile Val Asp Ile Ser Ile Lys
290 295 300

Gln Ala Pro Arg Val Gly Pro Ala Gly Glu His Arg Leu Val Thr Val
305 310 315 320

Thr Arg Thr Asp Asn Gln Ile Leu Glu Ala Glu Phe Pro Gly Leu Pro
325 330 335

Glu Ala Leu Ser Phe Val Ala Leu Val Asp Gly Tyr Phe Arg Leu Thr
340 345 350

Thr Asp Ser Gln His Phe Phe Cys Lys Glu Val Asp Pro Arg Leu Leu
355 360 365

Glu Glu Val Ala Glu Gln Cys His Gly Pro Ile Thr Leu Asp Phe Ala
370 375 380

Ile Asn Lys Leu Lys Thr Gly Gly Ser Arg Pro Gly Ser Tyr Val Leu
385 390 395 400

Arg Arg Ile Pro Gln Asp Phe Asp Ser Phe Leu Leu Thr Val Cys Val
405 410 415

Gln Asn Pro Leu Gly Pro Asp Tyr Lys Gly Cys Leu Ile Arg Arg Ser
420 425 430

Pro Thr Gly Thr Phe Leu Leu Val Gly Leu Ser Arg Pro His Ser Ser
435 440 445

Leu Arg Glu Leu Leu Ala Thr Cys Trp Asp Gly Gly Leu His Val Asp
450 455 460

Gly Val Ala Val Thr Leu Thr Ser Cys Cys Ile Pro Arg Pro Lys Glu
465 470 475 480

Lys Ser Asn Leu Ile Val Val Gln Arg Gly His Ser Pro Pro Thr Ser
485 490 495

Ser Leu Val Gln Pro Gln Ser Gln Tyr Gln Leu Ser Gln Met Thr Phe
500 505 510

His Lys Ile Pro Ala Asp Ser Leu Glu Trp His Glu Asn Leu Gly His
515 520 525

Gly Ser Phe Thr Lys Ile Tyr Arg Gly Cys Arg His Glu Val Val Asp
530 535 540

Gly Glu Ala Arg Lys Thr Glu Val Leu Leu Lys Val Met Asp Ala Lys
545 550 555 560

His Lys Asn Cys Met Glu Ser Phe Leu Glu Ala Ala Ser Leu Met Ser
565 570 575

Gln Val Ser Tyr Arg His Leu Val Leu Leu His Gly Val Cys Met Ala
580 585 590

Gly Asp Ser Thr Met Val Glu Glu Phe Val His Leu Gly Ala Ile Asp
595 600 605

Met Tyr Leu Arg Lys Arg Gly His Leu Val Pro Ala Ser Trp Lys Leu
610 615 620

Gln Val Val Lys Gln Leu Ala Tyr Ala Leu Asn Tyr Leu Glu Asp Lys
625 630 635 640

Gly Leu Ser His Gly Asn Val Ser Ala Arg Lys Val Leu Leu Ala Arg
645 650 655

Glu Gly Ala Asp Gly Ser Pro Pro Phe Ile Lys Leu Ser Asp Pro Gly
660 665 670

Val Ser Pro Ala Val Leu Ser Leu Glu Met Leu Thr Asp Arg Ile Pro
675 680 685

Trp Val Ala Pro Glu Cys Leu Arg Glu Ala Gln Thr Leu Ser Leu Glu
690 695 700

Ala Asp Lys Trp Gly Phe Gly Ala Thr Val Trp Glu Val Phe Ser Gly
705 710 715 720

Val Thr Met Pro Ile Ser Ala Leu Asp Pro Ala Lys Lys Leu Gln Phe
725 730 735

Tyr Glu Asp Arg Gln Gln Leu Ser Ala Pro Lys Trp Thr Glu Leu Ala
740 745 750

Leu Leu Ile Gln Gln Cys Met Ala Tyr Glu Pro Val Gln Arg Pro Ser
755 760 765

Leu Arg Ala Val Ile Arg Asp Leu Asn Ser Leu Ile Ser Ser Asp Tyr
770 775 780

Glu Leu Leu Ser Asp His Thr Trp Cys Pro Gly Thr Arg Asp Gly Leu
785 790 795 800

Trp Asn Gly Ala Gln Leu Tyr Ala Cys Gln Asp Pro Thr Ile Phe Glu
805 810 815

Glu Arg His Leu Lys Tyr Ile Ser Gln Leu Gly Lys Gly Phe Phe Gly
820 825 830

Ser Val Glu Leu Cys Arg Tyr Asp Pro Leu Gly Asp Asn Thr Gly Ala
835 840 845

Leu Val Ala Val Lys Gln Leu Gln His Ser Gly Pro Asp Gln Gln Arg
850 855 860

Asp Phe Gln Arg Glu Ile Gln Ile Leu Lys Ala Gln His Ser Asp Phe
865 870 875 880

Ile Val Lys Tyr Arg Gly Val Ser Tyr Gly Pro Gly Arg Gln Ser Pro
885 890 895

Ala Leu Val Met Glu Tyr Leu Pro Ser Gly Cys Leu Arg Asp Phe Leu
900 905 910

Gln Arg His Arg Gly Leu Asp Ala Ser Arg Leu Leu Leu Tyr Ser Ser
915 920 925

Gln Ile Cys Lys Gly Met Glu Tyr Leu Gly Ser Arg Arg Cys Val His
930 935 940

Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Glu Ser Glu Ala His Val
945 950 955 960

Lys Ile Ala Asp Phe Gly Leu Ala Lys Leu Leu Pro Leu Asp Lys Asp
965 970 975

Tyr Tyr Val Val Arg Glu Pro Gly Gln Ser Pro Ile Phe Trp Tyr Ala
980 985 990

Pro Glu Ser Leu Ser Asp Asn Ile Phe Ser Arg Gln Ser Asp Val Trp
995 1000 1005

Ser Phe Gly Val Val Leu Tyr Glu Leu Phe Thr Tyr Cys Asp Lys Ser
1010 1015 1020

Cys Ser Pro Ser Ala Glu Phe Leu Arg Met Met Gly Cys Glu Arg Asp
1025 1030 1035 1040

Val Pro Arg Leu Cys Arg Leu Leu Glu Leu Leu Glu Glu Gly Gln Arg
1045 1050 1055

Leu Pro Ala Pro Pro Cys Cys Pro Ala Glu Val Ser Cys Tyr Ser Gly
1060 1065 1070

```
Trp Arg Asp Asp Ile Cys Leu Pro Ala Glu
        1075                1080
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1100 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Met Ala Pro Pro Ser Glu Glu Thr Pro Leu Ile Ser Gln Arg Ser Cys
1               5                   10                  15

Ser Leu Ser Ser Ser Glu Ala Gly Ala Leu His Val Leu Leu Pro Pro
            20                  25                  30

Arg Gly Pro Gly Pro Pro Gln Arg Leu Ser Phe Ser Phe Gly Asp Tyr
        35                  40                  45

Leu Ala Glu Asp Leu Cys Val Arg Ala Ala Lys Ala Cys Gly Ile Leu
    50                  55                  60

Pro Val Tyr His Ser Leu Phe Ala Leu Ala Thr Glu Asp Leu Ser Cys
65                  70                  75                  80

Trp Phe Pro Pro Ser His Ile Phe Ser Ile Glu Asp Val Asp Thr Gln
                85                  90                  95

Val Leu Val Tyr Arg Leu Arg Phe Tyr Phe Pro Gly Trp Phe Gly Leu
            100                 105                 110

Glu Thr Cys His Arg Phe Gly Leu His Lys Asp Leu Thr Ser Ala Ile
        115                 120                 125

Leu Asp Val His Val Leu Glu His Leu Phe Ala Gln His Arg Ser Asp
    130                 135                 140

Leu Val Ser Gly Arg Leu Pro Val Gly Leu Ser Leu Lys Asp Gln Gly
145                 150                 155                 160

Glu Phe Leu Ser Leu Ala Val Leu Asp Leu Ala Gln Met Ala Arg Lys
                165                 170                 175

Gln Ala Gln Arg Pro Gly Glu Leu Leu Lys Ser Val Ser Tyr Lys Ala
            180                 185                 190

Cys Leu Pro Pro Ser Leu Arg Asp Leu Ile Gln Gly Gln Ser Phe Val
        195                 200                 205

Thr Arg Arg Arg Ile Arg Arg Thr Val Val Gln Ala Leu Ala Pro Cys
    210                 215                 220

Ser Ser Leu Pro Ser Arg Pro Tyr Ala Leu Met Ala Lys Tyr Ile Leu
225                 230                 235                 240

Asp Leu Glu Arg Leu His Pro Ala Ala Thr Thr Glu Ser Phe Leu Val
                245                 250                 255

Gly Leu Pro Gly Ala Gln Glu Glu Pro Gly Cys Leu Arg Val Thr Gly
            260                 265                 270

Asp Asn Gly Ile Ala Trp Ser Ser Lys Asp Gln Glu Leu Phe Gln Thr
        275                 280                 285
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Phe Cys Asp Phe Pro Glu Ile Val Asp Val Ser Ile Lys Gln Ala Pro
    290                 295                 300

Arg Val Gly Pro Ala Gly Glu His Arg Leu Val Thr Ile Thr Arg Met
305                 310                 315                 320

Asp Gly His Ile Leu Glu Ala Glu Phe Pro Gly Leu Pro Glu Ala Leu
                325                 330                 335

Ser Phe Val Ala Leu Val Asp Gly Tyr Phe Arg Leu Ile Cys Asp Ser
            340                 345                 350

Arg His Phe Phe Cys Lys Glu Val Ala Pro Pro Arg Leu Leu Glu Glu
        355                 360                 365

Glu Ala Glu Leu Cys His Gly Pro Ile Thr Leu Asp Phe Ala Ile His
    370                 375                 380

Lys Leu Lys Ala Ala Gly Ser Leu Pro Gly Ser Tyr Ile Leu Arg Arg
385                 390                 395                 400

Ser Pro Gln Asp Tyr Asp Ser Phe Leu Leu Thr Ala Cys Val Gln Thr
                405                 410                 415

Pro Leu Gly Pro Asp Tyr Lys Gly Cys Leu Ile Arg Gln Asp Pro Ser
            420                 425                 430

Gly Ala Phe Ser Leu Val Gly Leu Ser Gln Leu His Arg Ser Leu Gln
        435                 440                 445

Glu Leu Leu Thr Ala Cys Trp His Ser Gly Leu Gln Val Asp Gly Thr
    450                 455                 460

Ala Leu Asn Leu Thr Ser Cys Cys Val Pro Arg Pro Lys Glu Lys Ser
465                 470                 475                 480

Asn Leu Ile Val Val Arg Arg Gly Arg Asn Pro Thr Pro Ala Pro Gly
                485                 490                 495

His Ser Pro Ser Cys Cys Ala Leu Thr Lys Leu Ser Phe His Thr Ile
            500                 505                 510

Pro Ala Asp Ser Leu Glu Trp His Glu Asn Leu Gly His Gly Ser Phe
        515                 520                 525

Thr Lys Ile Phe His Gly His Arg Arg Glu Val Val Asp Gly Glu Thr
    530                 535                 540

His Asp Thr Glu Val Leu Leu Lys Val Met Asp Ser Arg His Gln Asn
545                 550                 555                 560

Cys Met Glu Ser Phe Leu Glu Ala Ala Ser Leu Met Ser Gln Val Ser
                565                 570                 575

Tyr Pro His Leu Val Leu Leu His Gly Val Cys Met Ala Gly Asp Ser
            580                 585                 590

Ile Met Val Gln Glu Phe Val Tyr Leu Gly Ala Ile Asp Thr Tyr Leu
        595                 600                 605

Arg Lys Arg Gly His Leu Val Pro Ala Ser Trp Lys Leu Gln Val Thr
    610                 615                 620

Lys Gln Leu Ala Tyr Ala Leu Asn Tyr Leu Glu Asp Lys Gly Leu Pro
625                 630                 635                 640

His Gly Asn Val Ser Ala Arg Lys Val Leu Leu Ala Arg Glu Gly Val
                645                 650                 655

Asp Gly Asn Pro Pro Phe Ile Lys Leu Ser Asp Pro Gly Val Ser Pro
            660                 665                 670
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Thr Val Leu Ser Leu Glu Met Leu Thr Asp Arg Ile Pro Trp Val Ala
        675                 680                 685

Pro Glu Cys Leu Gln Glu Ala Gly Thr Leu Asn Leu Glu Ala Asp Lys
    690                 695                 700

Trp Gly Phe Gly Ala Thr Thr Trp Glu Val Phe Ser Gly Ala Pro Met
705                 710                 715                 720

His Ile Thr Ser Leu Glu Pro Ala Lys Lys Leu Lys Phe Tyr Glu Asp
                725                 730                 735

Arg Gly Gln Leu Pro Ala Leu Lys Trp Thr Glu Leu Glu Gly Leu Ile
            740                 745                 750

Ala Gln Cys Met Ala Tyr Asp Pro Gly Arg Arg Pro Ser Phe Arg Ala
        755                 760                 765

Ile Leu Arg Asp Leu Asn Gly Leu Ile Thr Ser Asp Tyr Glu Leu Leu
    770                 775                 780

Ser Asp Pro Thr Pro Gly Ile Pro Asn Pro Arg Asp Glu Leu Cys Gly
785                 790                 795                 800

Gly Ala Gln Leu Tyr Ala Cys Gln Asp Pro Ala Ile Phe Glu Glu Arg
                805                 810                 815

His Leu Lys Tyr Ile Ser Leu Leu Gly Lys Gly Asn Phe Gly Ser Val
            820                 825                 830

Glu Leu Cys Arg Tyr Asp Pro Leu Gly Asp Asn Thr Gly Pro Leu Val
        835                 840                 845

Ala Val Lys Gln Leu Gln His Ser Gly Pro Glu Gln Gln Arg Asp Phe
    850                 855                 860

Gln Arg Glu Ile Gln Ile Leu Lys Ala Leu His Cys Asp Phe Ile Val
865                 870                 875                 880

Lys Tyr Arg Gly Val Ser Tyr Gly Pro Gly Arg Gln Glu Leu Arg Leu
                885                 890                 895

Val Met Glu Tyr Leu Pro Ser Gly Cys Leu Arg Asp Phe Leu Gln Arg
            900                 905                 910

His Arg Ala Arg Leu His Asn Asp Arg Leu Leu Leu Phe Ala Trp Gln
        915                 920                 925

Ile Cys Lys Gly Met Glu Tyr Leu Gly Ala Arg Arg Cys Val His Arg
    930                 935                 940

Asp Leu Ala Ala Arg Asn Ile Leu Val Glu Ser Glu Ala His Val Lys
945                 950                 955                 960

Ile Ala Asp Phe Gly Leu Ala Lys Leu Leu Pro Leu Gly Lys Asp Tyr
                965                 970                 975

Tyr Val Val Arg Val Pro Gly Gln Ser Pro Ile Phe Trp Tyr Ala Pro
            980                 985                 990

Glu Ser Leu Ser Asp Asn Ile Phe Ser Arg Gln Ser Asp Val Trp Ser
        995                 1000                1005

Phe Gly Val Val Leu Tyr Glu Leu Phe Thr Tyr Ser Asp Lys Ser Cys
    1010                1015                1020

Ser Pro Ser Thr Glu Phe Leu Arg Met Ile Gly Pro Glu Arg Glu Gly
1025                1030                1035                1040

Ser Pro Leu Cys His Leu Leu Glu Leu Leu Ala Glu Gly Arg Arg Leu
                1045                1050                1055
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Pro Pro Pro Ser Thr Cys Pro Thr Glu Val Gln Glu Leu Met Gln Leu
            1060                1065                1070

Cys Trp Ser Pro Asn Pro Gln Asp Arg Pro Ala Phe Asp Thr Leu Ser
        1075                1080                1085

Pro Gln Leu Asp Ala Leu Trp Arg Gly Ser Pro Gly
    1090                1095                1100
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 846 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Met Ala Pro Pro Ser Glu Glu Thr Pro Leu Ile Gln Arg Ser Cys Ser
1               5                   10                  15

Leu Ser Glu Ala Gly Ala Leu His Val Leu Leu Pro Arg Gly Pro Gly
            20                  25                  30

Pro Pro Gln Arg Leu Ser Phe Ser Phe Gly Asp Leu Ala Glu Asp Leu
        35                  40                  45

Cys Val Ala Ala Lys Ala Ile Leu Pro Val Tyr His Ser Leu Phe Ala
    50                  55                  60

Leu Ala Thr Glu Asp Leu Ser Cys Trp Phe Pro Gln Val Leu Tyr Arg
65                  70                  75                  80

Arg Phe Tyr Phe Pro Trp Phe Gly Leu Glu Cys His Arg Phe Gly Leu
                85                  90                  95

Lys Asp Leu Ser Ala Ile Leu Asp Val Leu Glu His Leu Phe Ala Gln
            100                 105                 110

His Arg Ser Asp Leu Val Ser Gly Arg Leu Pro Gly Leu Ser Leu Lys
        115                 120                 125

Gln Gly Glu Leu Ser Leu Ala Val Leu Asp Leu Ala Met Ala Arg Gln
    130                 135                 140

Ala Gln Arg Gly Glu Leu Leu Lys Val Ser Tyr Lys Ala Cys Leu Pro
145                 150                 155                 160

Pro Ser Leu Arg Asp Leu Ile Gln Gly Ser Phe Val Thr Arg Arg Ile
                165                 170                 175

Arg Arg Thr Val Leu Leu Met Ala Lys Tyr Ile Asp Leu Glu Arg Leu
            180                 185                 190

Pro Ala Glu Phe Val Gly Leu Pro Gly Ala Gly Arg Val Gly Asp Gly
        195                 200                 205

Ile Ala Trp Gln Glu Gln Phe Cys Asp Phe Pro Glu Ile Val Asp Ser
    210                 215                 220

Ile Lys Gln Ala Pro Arg Val Gly Pro Ala Gly Glu His Arg Leu Val
225                 230                 235                 240

Thr Thr Arg Asp Ile Leu Glu Ala Glu Phe Pro Gly Leu Pro Glu Ala
                245                 250                 255
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Leu Ser Phe Val Ala Leu Val Asp Gly Tyr Phe Arg Leu Asp Ser His
            260                 265                 270

Phe Phe Cys Lys Glu Val Pro Arg Leu Leu Glu Glu Ala Glu Cys His
        275                 280                 285

Gly Pro Ile Thr Leu Asp Phe Ala Ile Lys Leu Lys Gly Ser Pro Gly
    290                 295                 300

Ser Tyr Leu Arg Arg Pro Gln Asp Asp Ser Phe Leu Leu Thr Cys Val
305                 310                 315                     320

Gln Pro Leu Gly Pro Asp Tyr Lys Gly Cys Leu Ile Arg Pro Gly Phe
                325                 330                 335

Leu Val Gly Leu Ser His Ser Leu Glu Leu Leu Cys Trp Gly Leu Val
            340                 345                 350

Asp Gly Ala Leu Thr Ser Cys Cys Pro Arg Pro Lys Glu Lys Ser Asn
        355                 360                 365

Leu Ile Val Val Arg Gly Pro Thr Ser Leu Phe His Ile Pro Ala Asp
    370                 375                 380

Ser Leu Glu Trp His Glu Asn Leu Gly His Gly Ser Phe Thr Lys Ile
385                 390                 395                     400

Gly Arg Glu Val Val Asp Gly Glu Thr Glu Val Leu Leu Lys Val Met
                405                 410                 415

Asp His Asn Cys Met Glu Ser Phe Leu Glu Ala Ala Ser Leu Met Ser
            420                 425                 430

Gln Val Ser Tyr His Leu Val Leu Leu His Gly Val Cys Met Ala Gly
        435                 440                 445

Asp Ser Met Val Glu Phe Val Leu Gly Ala Ile Asp Tyr Leu Arg Lys
    450                 455                 460

Arg Gly His Leu Val Pro Ala Ser Trp Lys Leu Gln Val Lys Gln Leu
465                 470                 475                     480

Ala Tyr Ala Leu Asn Tyr Leu Glu Asp Lys Gly Leu His Gly Asn Val
                485                 490                 495

Ser Ala Arg Lys Val Leu Leu Ala Arg Glu Gly Asp Gly Pro Pro Phe
            500                 505                 510

Ile Lys Leu Ser Asp Pro Gly Val Ser Pro Val Leu Ser Leu Glu Met
        515                 520                 525

Leu Thr Asp Arg Ile Pro Trp Val Ala Pro Glu Cys Leu Glu Ala Thr
    530                 535                 540

Leu Leu Glu Ala Asp Lys Trp Gly Phe Gly Ala Thr Trp Glu Val Phe
545                 550                 555                     560

Ser Gly Met Ile Leu Pro Ala Lys Lys Leu Phe Tyr Glu Asp Arg Gln
                565                 570                 575

Leu Ala Lys Trp Thr Glu Leu Leu Ile Gln Cys Met Ala Tyr Pro Arg
            580                 585                 590

Pro Ser Arg Ala Arg Asp Leu Asn Leu Ile Ser Asp Tyr Glu Leu Leu
        595                 600                 605

Ser Asp Thr Pro Arg Asp Leu Gly Ala Gln Leu Tyr Ala Cys Gln Asp
    610                 615                 620

Pro Ile Phe Glu Glu Arg His Leu Lys Tyr Ile Ser Leu Gly Lys Gly
625                 630                 635                     640
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Phe Gly Ser Val Glu Leu Cys Arg Tyr Asp Pro Leu Gly Asp Asn Thr
                645                 650                 655

Gly Leu Val Ala Val Lys Gln Leu Gln His Ser Gly Pro Gln Gln Arg
            660                 665                 670

Asp Phe Gln Arg Glu Ile Gln Ile Leu Lys Ala His Asp Phe Ile Val
        675                 680                 685

Lys Tyr Arg Gly Val Ser Tyr Gly Pro Gly Arg Gln Leu Val Met Glu
    690                 695                 700

Tyr Leu Pro Ser Gly Cys Leu Arg Asp Phe Leu Gln Arg His Arg Ala
705                 710                 715                     720

Leu Arg Leu Leu Leu Gln Ile Cys Lys Gly Met Glu Tyr Leu Gly Arg
                725                 730                 735

Arg Cys Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Glu Ser
            740                 745                 750

Glu Ala His Val Lys Ile Ala Asp Phe Gly Leu Ala Lys Leu Leu Pro
        755                 760                 765

Leu Lys Asp Tyr Tyr Val Val Arg Pro Gly Gln Ser Pro Ile Phe Trp
    770                 775                 780

Tyr Ala Pro Glu Ser Leu Ser Asp Asn Ile Phe Ser Arg Gln Ser Asp
785                 790                 795                     800

Val Trp Ser Phe Gly Val Val Leu Tyr Glu Leu Phe Thr Tyr Asp Lys
                805                 810                 815

Ser Cys Ser Pro Ser Glu Phe Leu Arg Met Gly Glu Arg Leu Cys Leu
            820                 825                 830

Leu Glu Leu Leu Glu Gly Arg Leu Pro Pro Cys Pro Glu Val
        835                 840                 845
```

CLAIMS

1. A substantially pure JAK3 polypeptide consisting essentially of the amino acid sequence of FIGURE 1 (SEQ ID NO:2).

2. An isolated polynucleotide sequence consisting essentially of a polynucleotide sequence encoding a polypeptide having an amino acid sequence of FIGURE 1 (SEQ ID NO:2).

3. The isolated polynucleotide sequence of claim 2, consisting essentially of a polynucleotide sequence encoding a polypeptide having an amino acid sequence of FIGURE 1 (SEQ ID NO:2) and having at least one epitope for an antibody immunoreactive with JAK3.

4. The polynucleotide of claim 2, wherein the nucleotide sequence is selected from the group consisting of:
   a) FIGURE 1 (SEQ ID NO:1), wherein T can also be U;
   b) nucleic acid sequences complementary to a);
   c) fragments of a) or b) that are at least 15 bases in length and which will selectively hybridize to genomic DNA which encodes JAK3.

5. A host cell which contains the polynucleotide of claim 2 in an expression vector.

6. A recombinant expression vector which contains the polynucleotide of claim 2.

7. An antibody which binds to the polypeptide of FIGURE 1 (SEQ ID NO:2) and which binds with immunoreactive fragments of FIGURE 1 (SEQ ID NO:2).

8. The antibody of claim 7, wherein the antibody is polyclonal.

9. The antibody of claim 7, wherein the antibody is monoclonal.

10. A method for detecting a cell proliferative disorder associated with JAK3 in a subject, comprising contacting a target cellular component containing JAK3 with a reagent which detects JAK3.

11. The method of claim 10, wherein the target cellular component is nucleic acid.

12. The method of claim 11, wherein the nucleic acid is DNA.

13. The method of claim 11, wherein the nucleic acid is RNA.

14. The method of claim 11, wherein the nucleic acid is hypermethylated.

15. The method of claim 10, wherein the target cellular component is protein.

16. The method of claim 10, wherein the reagent is a probe.

17. The method of claim 16, wherein the probe is nucleic acid.

18. The method of claim 16, wherein the probe is an antibody.

19. The method of claim 18, wherein the antibody is polyclonal.

20. The method of claim 18, wherein the antibody is monoclonal.

21. The method of claim 16, wherein the probe is detectably labeled.

22. The method of claim 21, wherein the label is selected from the group consisting of a radioisotope, a bioluminescent compound, a chemiluminescent compound, a fluorescent compound, a metal chelate, or an enzyme.

23. The method of claim 10, wherein the cell proliferative disorder is associated with hematopoietic cells.

24. The method of claim 23, wherein the disorder is selected from the group consisting of leukemia, myelodysplasia, polyethemia vera, thrombocytosis, and aplastic anemia.

25. A method of treating a cell proliferative disorder associated with JAK3, comprising administering to a subject with the disorder, a therapeutically effective amount of reagent which modulates JAK3 expression.

26. The method of claim 25, wherein the reagent is a polynucleotide sequence comprising a JAK3 sense polynucleotide sequence.

27. The method of claim 26, wherein the reagent further includes is a polynucleotide sequence which encodes a promoter in operable linkage to the JAK3 polynucleotide sequence.

28. The method of claim 26, wherein the polynucleotide sequence is in an expression vector.

29. The method of claim 25, wherein the disorder is associated with hematopoietic cells.

30. The method of claim 29, wherein the disorder is selected from the group consisting of leukemia, myelodysplasia, polythemia vera, thrombocytosis, and aplastic anemia.

31. A method of gene therapy comprising introducing into cells of a host subject, an expression vector comprising a nucleotide sequence encoding JAK3, in operable linkage with a promoter.

32. The method of claim 31, wherein the expression vector is introduced into the subject's cells *ex vivo* and the cells are then reintroduced into the subject.

33. The method of claim 31, wherein the expression vector is an RNA virus.

34. The method of claim 33, wherein the RNA virus is a retrovirus.

35. The method of claim 31, wherein the subject is a human.

36. A diagnostic kit useful for the detection of a target cellular component indicative of a cell proliferative disorder associated with JAK3 comprising carrier means being compartmentalized to receive in close confinement therein one or more containers comprising a first container containing a probe for detection of JAK3 nucleic acid.

37. The kit of claim 36, wherein the target cellular component is a JAK3 polypeptide.

38. The kit of claim 37, wherein the probe is an antibody.

39. The kit of claim 36, wherein the target cellular component is a nucleic acid sequence.

40. The kit of claim 39, wherein the probe is a polynucleotide hybridization probe.

41. A method for stimulating hematopoietic cell proliferation comprising introducing into the cell a nucleotide sequence encoding JAK3 operatively linked to a promoter and inducing JAK3 gene expression.

42. The method of claim 41, wherein the nucleotide sequence encoding JAK3 comprises the sequence of FIGURE 1 (SEQ ID NO:1).

```
                        AAACAGTTAATACATATTTTTTATGTTACGTGTATTCTGTACAACAA
     AGTAAGCTAGACAAAAGAAAATGTTTTCTCCTTCCTGTGTGGACTTTCCTCTCGCTGCC
     TCCCGGCTCTGCCCGCCCTTCGAAAGTCCAGGGTCCCTGCCCGCTAGGCAAGTTGCACTC
  1  M  A  P  P  S  E  E  T  P  L  I  P  Q  R  S  C  S  L  L  S
     ATGGCACCTCCAAGTGAAGAGACGCCCCTGATCCCTCAGCGTTCATGCAGCCTCTTGTCC     60
 21  T  E  A  G  A  L  H  V  L  L  P  A  R  G  P  G  P  P  Q  R
     ACGGAGGCTGGTGCCCTGCATGTGCTGCTGCCCGCTCGGGGCCCCGGCCCCCCCAGCGC    120
 41  L  S  F  S  F  G  D  H  L  A  E  D  L  C  V  Q  A  A  K  A
     CTATCTTTCTCCTTTGGGGACCACTTGGCTGAGGACCTGTGCGTGCAGGCTGCCAAGGCC    180
 61  S  A  I  L  P  V  Y  H  S  L  F  A  L  A  T  E  D  L  S  C
     AGCGCGATCCTGCCTGTGTACCACTCCCTCTTTGCTCTGGCCACGGAGGACCTGTCCTGC    240
 81  W  F  P  R  A  T  S  S  P  W  R  M  P  A  P  Q  V  L  L  Y
     TGGTTCCCCCGAGCCACATCTTCTCCGTGGAGGATGCCAGCACCCCAAGTCCTGCTGTAC    300
101  R  I  R  P  Y  P  P  N  W  P  G  L  E  K  C  H  R  F  G  L
     AGGATTCGCTTTTACTTCCCCAATTGGTTTGGGCTGGAGAAGTGCCACCGCTTCGGGCTA    360
121  R  K  D  L  A  S  A  I  L  D  L  P  V  L  E  H  L  F  A  Q
     CGCAAGGATTTGGCCAGTGCTATCCTTGACCTGCCAGTCCTGGAGCACCTCTTTGCCCAG    420
141  H  R  S  D  L  V  S  G  R  L  P  R  G  L  S  L  K  E  Q  G
     CACCGCAGTGACCTGGTGAGTGGGCGCCTCCCCCGTGGCCTCAGTCTCAAGGAGCAGGGT    480
161  E  C  L  S  L  A  V  L  D  L  A  R  M  A  R  E  Q  A  Q  R
     GAGTGTCTCAGCCTGGCCGTGTTGGACCTGGCCCGGATGGCGCGAGAGCAGGCCCAGCGG    540
181  R  G  E  L  L  K  T  V  S  Y  K  A  C  L  P  P  S  L  R  D
     CGGGGAGAGCTGCTGAAGACTGTCAGCTACAAGGCCTGCCTACCCCCAAGCCTGCGCGAC    600
201  L  I  Q  G  L  S  F  V  T  G  R  R  I  R  R  T  V  E  S  P
     CTGATCCAGGGCCTGAGCTTCGTGACGGGGAGGCGTATTCGGAGGACGGTGGAGAGCCCC    660
221  L  R  R  V  A  A  C  Q  A  D  R  H  S  L  M  A  K  Y  I  M
     CTGCGCCGGGTGGCCGCCTGCCAGGCAGACCGGCACTCGCTCATGGCCAAGTACATCATG    720
241  D  L  E  R  L  D  P  A  G  A  A  E  T  F  H  V  G  L  P  G
     GACCTGGAGCGGCTGGATCCAGCCGGGGCCGCCGAGACCTTCCACGTGGGCCTCCCTGGG    780
261  A  L  G  G  H  D  G  L  G  L  V  R  V  A  G  D  G  G  I  A
     GCCCTTGGTGGCCACGACGGGCTGGGGCTCGTCCGCGTGGCTGGTGACGGCGGCATCGCC    840
281  W  T  Q  G  E  Q  E  V  L  Q  P  F  C  D  F  P  E  I  V  D
     TGGACCCAGGGAGAACAGGAGGTCCTCCAGCCCTTCTGCGACTTTCCAGAAATCGTAGAC    900
301  I  S  I  K  Q  A  P  R  V  G  P  A  G  E  H  R  L  V  T  V
     ATTAGCATCAAGCAGGCCCCGCGCGTTGGCCCGGCCGGAGAGCACCGCCTGGTCACTGTT    960
321  T  R  T  D  N  Q  I  L  E  A  E  F  P  G  L  P  E  A  L  S
     ACCAGGACAGACAACCAGATTTTAGAGGCCGAGTTCCCAGGGCTGCCCGAGGCTCTGTCG   1020
341  F  V  A  L  V  D  G  Y  F  R  L  T  T  D  S  Q  H  F  F  C
     TTCGTGGCGCTCGTGGACGGCTACTTCCGGCTGACCACGGACTCCCAGCACTTCTTCTGC   1080
361  K  E  V  D  P  R  L  L  E  E  V  A  E  Q  C  H  G  P  I  T
     AAGGAGGTGGACCCGAGGCTGCTGGAGGAAGTGGCCGAGCAGTGCCACGGCCCCATCACT   1140
381  L  D  F  A  I  N  K  L  K  T  G  G  S  R  P  G  S  Y  V  L
     CTGGACTTTGCCATCAACAAGCTCAAGACTGGGGGCTCACGTCCTGGCTCCTATGTTCTC   1200
401  R  R  I  P  Q  D  F  D  S  F  L  L  T  V  C  V  Q  N  P  L
     CGCCGCATCCCCCAGGACTTTGACAGCTTCCTCCTCACTGTCTGTGTCCAGAACCCCCTT   1260
421  G  P  D  Y  K  G  C  L  I  R  R  S  P  T  G  T  F  L  L  V
     GGTCCTGATTATAAGGGCTGCCTCATCCGGCGCAGCCCCACAGGAACCTTCCTTCTGGTT   1320
441  G  L  S  R  P  H  S  S  L  R  E  L  L  A  T  C  W  D  G  G
     GGCCTCAGCCGACCCCACAGCAGTCTTCGAGAGCTCCTGGCAACCTGCTGGGATGGGGGG   1380
461  L  H  V  D  G  V  A  V  T  L  T  S  C  C  I  P  R  P  K  E
     CTGCACGTAGATGGGGTGGCAGTGACCCTCACTTCCTGCTGTATCCCCAGACCCAAAGAA   1440
481  K  S  N  L  I  V  V  Q  R  G  H  S  P  P  T  S  S  L  V  Q
     AAGTCCAACCTGATTGTGGTCCAGAGAGGTCACAGCCCACCCACATCATCCTTGGTTCAG   1500
501  P  Q  S  Q  Y  Q  L  S  Q  M  T  F  H  K  I  P  A  D  S  L
     CCCCAATCCCAATACCAGCTGAGTCAGATGACATTTCACAAGATCCCTGCTGACAGCCTG   1560
521  E  W  H  E  N  L  G  H  G  S  F  T  K  I  Y  R  G  C  R  H
     GAGTGGCATGAGAACCTGGGCCATGGGTCCTTCACCAAGATTTACCGGGGCTGTCGCCAT   1620
541  E  V  V  D  G  E  A  R  K  T  E  V  L  L  K  V  M  D  A  K
     GAGGTGGTGGATGGGGAGGCCCGAAAGACAGAGGTGCTGCTGAAGGTCATGGATGCCAAG   1680
561  H  K  N  C  M  E  S  F  L  E  A  A  S  L  M  S  Q  V  S  Y
     CACAAGAACTGCATGGAGTCATTCCTGGAAGCAGCGAGCTTGATGAGCCAAGTGTCGTAC   1740
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581  R H L V L L H G V C M A G D S T M V E E
     CGGCATCTCGTGCTGCTCCACGGCGTGTGCATGGCTGGAGACAGCACCATGGTCGAGGAA  1800
601  F V H L G A I D M Y L R K R G H L V P A
     TTTGTACACCTGGGGGCCATAGACATGTATCTGCGAAAACGTGGCCACCTGGTGCCAGCC  1860
621  S W K L Q V V K Q L A Y A L N Y L E D K
     AGCTGGAAGCTGCAGGTGGTCAAACAGCTGGCCTACGCCCTCAACTATCTGGAGGACAAA  1920
641  G L S H G N V S A R K V L L A R E G A D
     GGCCTGTCCCATGGCAATGTCTCTGCCCGGAAGGTGCTCCTGGCTCGGGAGGGGGCTGAT  1980
661  G S P P F I K L S D P G V S P A V L S L
     GGGAGCCCGCCCTTCATCAAGCTGAGTGACCCTGGGGTCAGCCCCGCTGTGTTAAGCCTG  2040
681  E M L T D R I P W V A P E C L R E A Q T
     GAGATGCTCACCGACAGGATCCCCTGGGTGGCCCCCGAGTGTCTCCGGGAGGCGCAGACA  2100
701  L S L E A D K W G F G A T V W E V F S G
     CTTAGCTTGGAAGCTGACAAGTGGGGCTTCGGCGCCACGGTCTGGGAAGTGTTTAGTGGC  2160
721  V T M P I S A L D P A K K L Q F Y E D R
     GTCACCATGCCCATCAGTGCCCTAGATCCTGCTAAGAAACTCCAATTTTATGAGGACCGG  2220
741  Q Q L S A P K W T E L A L L I Q Q C M A
     CAGCAGCTGTCGGCCCCCAAGTGGACAGAGCTGGCCCTGCTGATTCAACAGTGCATGGCC  2280
761  Y E P V Q R P S L R A V I R D L N S L I
     TATGAGCCGGTCCAGAGGCCCTCCTTACGAGCCGTCATTCGTGACCTCAATAGTCTCATC  2340
781  S S D Y E L L S D H T W C P G T R D G L
     TCTTCAGACTATGAGCTCCTCTCAGACCACACCTGGTGCCCTGGCACTCGTGATGGGCTG  2400
801  W N G A Q L Y A C Q D P T I F E E R H L
     TGGAATGGTGCCCAGCTCTATGCCTGCCAAGACCCCACGATCTTCGAGGAGAGACACCTC  2460
821  K Y I S Q L G K G F F G S V E L C R Y D
     AAGTACATCTCACAGCTGGGCAAGGGCTTCTTTGGCAGCGTGGAGCTGTGCCGCTATGAC  2520
841  P L G D N T G A L V A V K Q L Q H S G P
     CCGCTAGGCGACAATACAGGTGCCCTGGTGGCCGTGAAACAGCTGCAGCACAGCGGGCCA  2580
861  D Q Q R D F Q R E I Q I L K A Q H S D F
     GACCAGCAGAGGGACTTTCAGCGGGAGATTCAGATCCTCAAAGCACAGCACAGTGATTTC  2640
881  I V K Y R G V S Y G P G R Q S P A L V M
     ATTGTCAAGTATCGTGGTGTCAGCTATGGCCCGGGCCGCCAGAGCCCTGCGCTGGTCATG  2700
901  E Y L P S G C L R D F L Q R H R G L D A
     GAGTACCTGCCCAGCGGCTGCTTGCGCGACTTCCTGCAGCGGCACCGGGGCCTCGATGCC  2760
921  S R L L L Y S S Q I C K G M E Y L G S R
     AGCCGCCTCCTTCTCTATTCCTCGCAGATCTGCAAGGGCATGGAGTACCTGGGCTCCCGC  2820
941  R C V H R D L A A R N I L V E S E A H V
     CGCTGCGTGCACCGCGACCTGGCCGCCCGAAACATCCTCGTGGAGAGCGAGGCACACGTC  2880
961  K I A D F G L A K L L P L D K D Y Y V V
     AAGATCGCTGACTTCGGCCTAGCTAAGCTGCTGCCGCTTGACAAAGACTACTACGTGGTC  2940
981  R E P G Q S P I F W Y A P E S L S D N I
     CGCGAGCCAGGCCAGAGCCCCATTTTCTGGTATGCCCCCGAATCCCTCTCGGACAACATC  3000
1001 F S R Q S D V W S F G V V L Y E L F T Y
     TTCTCTCGCCAGTCAGACGTCTGGAGCTTCGGGGTCGTCCTGTACGAGCTCTTCACCTAC  3060
1021 C D K S C S P S A E F L R M M G C E R D
     TGCGACAAAAGCTGCAGCCCCTCGGCCGAGTTCCTGCGGATGATGGGATGTGAGCGGGAT  3120
1041 V P R L C R L L E L L E E G Q R L P A P
     GTCCCCCGCCTCTGCCGCCTCTTGGAACTGCTGGAGGAGGGCCAGAGGCTGCCGGCGCCT  3180
1061 P C C P A E V S C Y S G W R D D I C L P
     CCTTGCTGCCCTGCTGAGGTGAGTTGCTACAGTGGCTGGAGAGACGACATCTGCCTGCCT  3240
1081 A E
     GCTGAGTGAGTTGCTACAGTGGCTGAGAGACGACATCTGCTCCATGGCTGGTGGCCGACA  3300
     GTAATCTCACGCCGGACCTGCCGCAGCCCCTGCCCCAGACCTCTCACCATCACCGCCACC  3360
     ACCGTGCAGCTGCCACCAACCCTGCACGCTACTGCTGCCTCAGTGGCTGTACCCAACAAG  3420
     ACCTGCTGACCCTCTGTCCCTACTGATTCCTCCTTGGGTGCAGCCTCAGAGTGCCTGAGG  3480
     CCCAGAGGGTCTGGTCTGGTGAGCTCCTGAGGCCACACAGCACCATAAAGTCTCGCATCT  3540
     ACAGGCCTTTGATTACCTCCTGGGATGGTGCTCACTATCTACCCCAGACCAACGCCACC  3600
     TGCAGCCTGTGGAGTCAACTGCAGAATAAATCACACCCTA
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FIG. 1 (PAGE 2 OF 2)

SUBSTITUTE SHEET (RULE 26)

```
      1                                                                                                   100
JAK3  MAPPSEETPLIPQRSCSLLSTEAGA..LHVLLPARGPGPPQR............LSFSFGDHLAEDLCVQAAKASAILPVYHSLFALATEDLSCWFPRAT
JAK2  MGMACLTMTEMEATSTSPVHQNGDIPGSANSVKQIEPVLQVYLYHSLGQAEGEYLKFPSGEYVAEEICVAASKACGITPVYHNMFALMSETERIWYPPNH
JAK1  MQYLNIKEDCNAMAFCAKMRSSKKTEVNLEAPEPGVEVIF.YL......SDREPLRLGSGEYTAEELCIRAAQACRISPLCHNLFALYDENTKLWYAPNR
TYK2  MPLRHWGMARGSKPVGDGAQPMAAMGGLKVLLHWAGPGGGEPW ..........VTFSESSLTAEEVCIHIAHKVGITPPCFNLFALFDAQAQVWLPPNH
CONS  M--------------------------------P----------------L----G---AEE-C--A--A--I-P--HNLFAL-------W-PPN-

      101                                                                                                 200
JAK3  SSPWRMPAPQVLLYRIRFYFPNWFGLEKCHRFGLRKDL..............ASAILDLPVLEHLFAQHRSDLVSGRLPRGLSLKEQG......ECLSLA
JAK2  VFHIDESTRHDILYRIRFYFPHWYCSGSSRTYRYGVSRGAEA............PLLDDFVMSYLFVQWRHDFVHGWIKVPVTHETQE......ECLGMA
JAK1  TITVDDKMSLRLHYRMRFYFTNWHGTNDNEQSVWRHSPKKQKNGYEKKKIPDATPLLDASSLEYLFAQGQYDLVKCLAPIRDPKTEQDGHDIENECLGMA
TYK2  ILEIPRDASLMLYFRIRFYFRNWHGMNPREPAVYRCGPPGTEASSD..QTAQGMQLLDPASFEYLFEQGKHEFVNDVASLWELSTEEEIHHFKNESLGMA
CON   -----------L-YRIRFYF-NW-G-----------------------------LLD----EYLF-Q---D-V-----------EQ-------ECLGMA

      201                                                                                                 300
JAK3  VLDLARMAREQAQRRGELLKTVSYKACLPPSLRDLIQGLSFVTGRRIRRTVESPLRRV.....AACQADRHSLMAKYIMDLERLDPAGAAETFHVGLPG.
JAK2  VLDMMRIAKEKDQTPLAVYNSVSYKTFLPKCVRAKIQDYHILTRKRIRYRFRRFIQQF.....SQCKATARNLKLKYLINLETLQSAFYTEQFEVKESAR
JAK1  VLAISHYAMMKKMQLPELPKDISYKRYIPETLNKSIRQRNLLTRMRINNVFKDFLKEFNNKTICDSSVSTHDLKVKYLATLETLTKHYGAEIFETSMLLI
TYK2  FLHLCHLALRHGIPLEEVAKKTSFKDCIPRSFRRHIRQHSALTRLRLRNVFRRFLRDFQ.....PGRLSQQMVMVKYLATLERLAPRFGTERVPVCHLRL
CONS  VL-----A--------E--K--SYK---P---R--I-----LTR-RIR--F--FL--F--------------LK-KYL--LE-L------E-F-V-----

      301                                                                                                 400
JAK3  .........................ALGGHDGLGLVRVAGDGGIAWTQGE..................................QEVLQPFCDFPE
JAK2  GPSGEEIFATIIIT......................GNGGIQWSRGKH.............................KESETLTEQDVQLYCDFPD
JAK1  SSENEMNWFHSND............GGNVLYYEVMVTGNLGIQWRHKPNVVSVEKE.........KNKLKRKKLENKDKKDEEKNKIREE.WNNFSFFPE
TYK2  LAQAEGEPCYIRDSGVAPTDPGPESAAGPPTHEVLVTGTGGIQWWPVEEEVNKEEGSSGSSGRNPQASLFGKKAKAHKAFGQPADRPREPLWAYFCDFRD
CONS  -----------------------------V-VTG-GGIQW-----------------------------------------E-----FCDFP-

      401                                                                                                 500
JAK3  IVDISIKQAPRVGPAGEHRLVTVTRTDNQILEAEFPGLPEALSFVALVDGYFRLTTDSQHFFCKEVD.PRLLEEVAEQCHGPITLDFAINKLKTGGSRPG
JAK2  IIDVSIKQANQ.ECSNESRIVTVHKQDGKVLEIELSSLKEALSFVSLIDGYYRLTADAHHYLCKEVAPPAVLENIHSNCHGPISMDFAISKLKKAGNQTG
JAK1  ITHIVIKE..........SVVSINKQDNKKMELKLSSHEEALSFVSLVDGYFRLTADAHHYLCTDVAPPLIVHNIQNGCHGPICTEYAINKLRQEGSEEG
TYK2  ITHVVLKE..........HCVSIHRQDNKCLELSLPSRAAALSFVSLVDGYFRLTADSSHYLCHEVAPPRLVMSIRDGIHGPLLEPFVQAKLR...PEDG
CONS  I----IK------------V----QDNK-LE--L-S--EALSFVSLVDGYFRLTAD--HYLC-EVAPP-----I---CHGPI---FAI-KL-------G
```

FIG. 2 (PAGE 1 OF 3)

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     501                                                                                                  600
JAK3 SYVLRRIPQDFDSFLLTVC.......VQNPLGPDYKGCLIRRSPTGTFLLVGLSRPHSSLRELLATCWDGGLHVDGVAVTLTSCCIPRPKEKSNLIVVQR
JAK2 LYVLRCSPKDFNKYFLTFA.......VERENVIEYKHCLITKNENGEYNLSGTNRNFSNLKDLLNCYQMETVRSDSIIFQFTKCCPPKPKDKSNLLVFRT
JAK1 MYVLRWSCTDFDNILMTVTCFEKSEQVQGAQK.QFKNFQI.EVQKGRYSLHGSDRSFPSLGDLMSHLKKQILRTDNISFMLKRCCQPKPREISNLLVATK
TYK2 LYLIHWSTSHPYRLILTVA..QRSQAPDGMQSLRLRKFPI.EQQDGAFVLEGWGRSFPSVRELGAALQGCLLRAGDDCFSLRRCCLPQPGETSNLII.MR
CONS -YVLRWS--DF----LTV--------V--------K---I-----G---L-G--R-F-SL--L---------R-D---F-L--CC-P-P---SNLLV---

     601                                                                                                  700
JAK3 GHSPPTSSLVQPQSQYQLSQMTFHKIPADSLEWHENLGHGSFTKIYRGCRHEVVD.GEARKTE...................VLLKVMDAKHKNCMESFL
JAK2 NGISDVQISPTLQRHNNVNQMVFHKIRNEDLIFNESLGQGTFTKIFKGVRREVGDYGQLHKTE...................VLLKVLDKAHRNYSESFF
JAK1 K.......AQEWQPVYPMSQLSFDRILKKDLVQGEHLGRGTRTHIYSGTLMDYKDDEGTSEEKK................IKVILKVLDPSHRDISLAFF
TYK2 G.......ARASPRTLNLSQLSFHRVDQKEITQLSHLGQGTRTNVYEGRLR..VEGSGDPEEGKMDDEDPLVPGRDRGQELRVVLKVLDPSHHDIALAFY
CONS -----------Q-----SQ--FH-I----L---E-LG-GT-T-IY-G------D------------------------V-LKVLD--H------F-
           ------> JH2
     701                                                                                                  800
JAK3 EAASLMSQVSYRHLVLLHGVCMAG.DSTMVEEFVHLGAIDMYLRKRGHLVPASWKLQVVKQLAYALNYLEDKGLSHGNVSARKVLLAREGA..DGSPPFI
JAK2 EAASMMSQLSHKHLVLNYGVCVCGEENILVQEFVKFGSLDTYLKKNKNSINILWKLGVAKQLAWAMHFLEEKSLIHGNVCAKNILLIREEDRRTGNPPFI
JAK1 EAASMMRQVSHKHIVYLYGVCVRDVENIMVEEFVEGGPLDLFMHRKSDVLTTPWKFKVAKQLASALSYLEDKDLVHGNVCTKNLLLAREGI.DSECGPFI
TYK2 ETASLMSQVSHTHLAFVHGVCVRGPENSMVTEYVEHGPLDVWLRRERGHVPMAWKMVVAQQLASALSYLENKNLVHGNVCGRNILLARLGL.AEGTSPFI
CONS EAAS-MSQVSH-HLV---GVCV-G-EN-MV-EFV--G-LD---R---------WK--VAKQLA-AL-YLEDL-L-HGNVC--NILLAREG-------PFI

     801                                                                                                  900
JAK3 KLSDPGVSPAVLSLEMLTDRIPWVAPECLREAQT.LSLEADKWGFGATVWEVFSGVTMPISALDPAKKLQFYEDRQQLSAPKWTELALLIQQCMAYEPVQ
JAK2 KLSDPGISITVLPKDILQERIPWVPPECIENPKN.LNLATDKWSFGTTLWEICSGGDKPLSALDSQRKLQFYEDKHQLPAPKWTELANLINNCMDYEPDF
JAK1 KLSDPGIPITVLSRQECIERIPWIAPECVEDSKN.LSVAADKWSFGTTLWEICYNGEIPLKDKTLIEKERFYESRCRPVTPSCKELADLMTRCMNYDPNQ
TYK2 KLSDPGVGLGALSREERVERIPWLAPECLPGGANSLSTAMDKWGFGATLLEICFDGEAPLQSRSPSEKEHFYQRQHRLPEPSCPQLATLTSQCLTYEPTQ
CONS KLSDPG----VLS-----ERIPW-APEC-----N-LS-A-DKW-FG-TLWEOC--G--PL-------K--FYE----L--P---ELA-L---CM-YEP-Q
```

FIG. 2 (PAGE 2 OF 3)

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      901                                                                                                 1000
JAK3  RPSLRAVIRDLNSLISSDYELLSDHTWCPGTRDGLWNGAQLYACQ.DPTIFEERHLKYISQLGKGFFGSVELCRYDPLGDNTGALVAVKQLQ.HSGPDQQ
JAK2  RPAFRAVIRDLNSLFTPDYELLTENDMLPNMRIGALGFSGAFEDR.DPTQFEERHLKFLQQLGKGNFGSVEMCRYDPLQDNTGEVVAVKKLQ.HSTEEHL
JAK1  RPFFRAIMRDINKLEEQNPDIVSRKKNQPTEV..............DPTHFEKRFLKRIRDLGEGHFGKVELCRYDP.EDNTGEQVAVKSLKPESGGNHI
TYK2  RPSFRTILRDLTRVQPHNLADVLTVNRDSPAV..............GPTTFHKRYLKKIRDLGEGHFGKVSLYCYDPTNDGTGEMVAVKALKADCGPQHR
CONS  RP-FRA--RDLN-L--------------P----------------DPT-FE-R-LKOI--LG-G-FG-VELCRYDP--DNTGE-VAVK-L---SG--H-
                JH2 <--------                  --------> JH1
      1001                                                                                                1100
JAK3  RDFQREIQILKAQHSDFIVKYRGVSYGPGRQSPALVMEYLPSGCLRDFLQRHRG.LDASRLLLYSSQICKGMEYLGSRRCVHRDLAARNILVESEAHVKI
JAK2  RDFEREIEILKSLQHDNIVKYKGVCYSAGRRNLRLIMEYLPYGSLRDYLQKHKERIDHKKLLQYTSQICKGMEYLGTKRYIHRDLATRNILVENENRVKI
JAK1  ADLKKEIEILRNLYHENIVKYKGICTEDGGNGIKLIMEFLPSGSLKEYLPKNKNKINLKQQLKYAVQICKGMDYLGSRQYVHRDLAARNVLVESEHQVKI
TYK2  SGWKQEIDILRTLYHEHIIKYKGCCEDQGEKSLQLVMEYVPLGSLRDYLP..RHSIGLAQLLLFAQQICEGMAYLHAHDYIHRDLAARNVLLDNDRLVKI
CONS  -D---EI-IL--L-H--IVKYKG-C---G-----L-MEYLP-GSLRDYL------I----LLLYLLQICKGM-YLG---Y-HRDLAARN-LVE-E--VKI

      1101                                                                                                1200
JAK3  ADFGLAKLLPLDKDYYVVREPGQSPIFWYAPESLSDNIFSRQSDVWSFGVVLYELFTYCDKSCSPSAEFLRMMGCERDVPRLC.RLLELLEEGQRLPAPP
JAK2  GDFGLTKVLPQDKEYYKVKEPGESPIFWYAPQSLTESKFSVASDVWSFGVVLYELFTYIEKSKSPPVEFMRMIGNDKQGQMIVFHLIELLKSNGRLPRPE
JAK1  GDFGLTKAIETDKEYYTVKDDRDSPVFWYAPECLMQSKFYIASDVWSFGVTLHELLTYCDSDSSPMALFLKMIGPT.HGQMTVTRLVNTLKEGKRLPCPP
TYK2  GDFGLAKAVPEGHEYYRVREDGDSPVFWYAPECLKEYKFYYASDVWSFGVTLYELLTHCDSSQSPPTKFLELIGIA.QGQMTVLRLTELLERGERLPRPD
CONS  GDFGL-K--P-DKEYY-V-E-G-SP-FWYAPE-L---LF--ASDVWSFGV-LYEL-TYCD-S-SP---FL-MIG----GQM-V-RL-ELL--G-RLP-P-

      1201                                         1249
JAK3  CCPAEVSCYSGWRDDICLPAE........................
JAK2  GCPDEIYVIMTECWNNNVSQRPSFRDLSFGWIKCGTV.........
JAK1  NCPDEVYQLMRKCWEFQPSNRTSFQNLIEGFEALLK..........
TYK2  KCPCEVYHLMKNCWETEASFRPTFENLIPILKTVHEKYQGQAPSVFSVC
CONS  -CP-EVY-LM--CW----S-R--F--L--------------------
                JH1 <--------
```

FIG. 2 (PAGE 3 OF 3)

```
hJAK3      1 MAPPSEETPLIPQRSCSLLSTEAGALHVLLPARGPGPPQRLSFSFGDHLAEDLCVQAAKA  60
rJAK3      1 MAPPSEETPLISQRSCSLSSSEAGALHVLLPPRGPGPPQRLSFSFGDYLAEDLCVRAAKA  60
CONS         MAPPSEETPLI QRSCSL S+EAGALHVLLP RGPGPPQRLSFSFGD+LAEDLCV+AAKA

hJAK3     61 SAILPVYHSLFALATEDLSCWFPRATSSPWRMPAPQVLLYRIRFYFPNWFGLEKCHRFGL 120
rJAK3     61 CGILPVYHSLFALATEDLSCWFPPSHIFSIEDVDTQVLVYRLRFYFPGWFGLETCHRFGL 120
CONS           ILPVYHSLFALATEDLSCWFP +         QVL+YR+RFYFP WFGLE CHRFGL

hJAK3    121 RKDLASAILDLPVLEHLFAQHRSDLVSGRLPRGLSLKEQGECLSLAVLDLARMAREQAQR 180
rJAK3    121 HKDLTSAILDVHVLEHLFAQHRSDLVSGRLPVGLSLKDQGEFLSLAVLDLAQMARKQAQR 180
CONS          KDL SAILD+ VLEHLFAQHRSDLVSGRLP GLSLK+QGE LSLAVLDLA+MAR+QAQR

hJAK3    181 RGELLKTVSYKACLPPSLRDLIQGLSFVTGRRIRRTVESPLRRVAACQADRHSLMAKYIM 240
rJAK3    181 PGELLKSVSYKACLPPSLRDLIQGQSFVTRRRIRRTVVQALAPCSSLPSRPYALMAKYIL 240
CONS          GELLK+VSYKACLPPSLRDLIQG SFVT RRIRRTV   L    ++   +   ++LMAKYI+

hJAK3    241 DLERLDPAGAAETFHVGLPGALGGHDGLGLVRVAGDGGIAWTQGEQEVLQPFCDFPEIVD 300
rJAK3    241 DLERLHPAATTESFLVGLPGAQEEP...GCLRVTGDNGIAWSSKDQELFQTFCDFPEIVD 297
CONS         DLERL PA   E+F VGLPGA       G  RV GD GIAW+  +QE+ Q FCDFPEIVD

hJAK3    301 ISIKQAPRVGPAGEHRLVTVTRTDNQILEAEFPGLPEALSFVALVDGYFRLTTDSQHFFC 360
rJAK3    298 VSIKQAPRVGPAGEHRLVTITRMDGHILEAEFPGLPEALSFVALVDGYFRLICDSRHFFC 357
CONS         +SIKQAPRVGPAGEHRLVT+TR D  ILEAEFPGLPEALSFVALVDGYFRL  DS+HFFC

hJAK3    361 KEVDP.RLLEEVAEQCHGPITLDFAINKLKTGGSRPGSYVLRRIPQDFDSFLLTVCVQNP 419
rJAK3    358 KEVAPPRLLEEEAELCHGPITLDFAIHKLKAAGSLPGSYILRRSPQDYDSFLLTACVQTP 417
CONS         KEV P RLLEE AE CHGPITLDFAI+KLK  GS PGSY+LRR PQD+DSFLLT CVQ P

hJAK3    420 LGPDYKGCLIRRSPTGTFLLVGLSRPHSSLRELLATCWDGGLHVDGVAVTLTSCCIPRPK 479
rJAK3    418 LGPDYKGCLIRQDPSGAFSLVGLSQLHRSLQELLTACWHSGLQVDGTALNLTSCCVPRPK 477
CONS         LGPDYKGCLIR+ P+G F LVGLS+ H SL+ELL  CW  GL VDG A+ LTSCC+PRPK

hJAK3    480 EKSNLIVVQRGHSPPTSSLVQPQSQYQLSQMTFHKIPADSLEWHENLGHGSFTKIYRGCR 539
rJAK3    478 EKSNLIVVRRGRN PTPAPGHSPSCCALTKLSFHTIPADSLEWHENLGHGSFTKIFHGHR 537
CONS         EKSNLIVV+RG + PT +     S   L++++FH IPADSLEWHENLGHGSFTKI+ G R
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FIG. 3 (PAGE 1 OF 2)

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hJAK3    540 HEVVDGEARKTEVLLKVMDAKHKNCMESFLEAASLMSQVSYRHLVLLHGVCMAGDSTMVE 599
rJAK3    538 REVVDGETHDTEVLLKVMDSRHQNCMESFLEAASLMSQVSYPHLVLLHGVCMAGDSIMVQ 597
CONS          EVVDGE   TEVLLKVMD++H+NCMESFLEAASLMSQVSY HLVLLHGVCMAGDS MV+

hJAK3    600 EFVHLGAIDMYLRKRGHLVPASWKLQVVKQLAYALNYLEDKGLSHGNVSARKVLLAREGA 659
rJAK3    598 EFVYLGAIDTYLRKRGHLVPASWKLQVTKQLAYALNYLEDKGLPHGNVSARKVLLAREGV 657
CONS         EFV+LGAID YLRKRGHLVPASWKLQV KQLAYALNYLEDKGL HGNVSARKVLLAREG

hJAK3    660 DGSPPFIKLSDPGVSPAVLSLEMLTDRIPWVAPECLREAQTLSLEADKWGFGATVWEVFS 719
rJAK3    658 DGNPPFIKLSDPGVSPTVLSLEMLTDRIPWVAPECLQEAGTLNLEADKWGFGATTWEVFS 717
CONS         DG+PPFIKLSDPGVSP VLSLEMLTDRIPWVAPECL+EA TL+LEADKWGFGAT WEVFS

hJAK3    720 GVTMPISALDPAKKLQFYEDRQQLSAPKWTELALLIQQCMAYEPVQRPSLRAVIRDLNSL 779
rJAK3    718 GAPMHITSLEPAKKLKFYEDRGQLPALKWTELEGLIAQCMAYDPGRRPSFRAILRDLNGL 777
CONS         G  M I++L+PAKKL+FYEDR QL A KWTEL  LI QCMAY+P +RPS RA++RDLN L

hJAK3    774 ISSDYELLSDHTW.CPGTRDGLWNGAQLYACQDPTIFEERHLKYISQLGKGFFGSVELCR 838
rJAK3    778 ITSDYELLSDPTPGIPNPRDELCGGAQLYACQDPAIFEERHLKYISLLGKGNFGSVELCR 837
CONS         I+SDYELLSD T    P  RD L  GAQLYACQDP IFEERHLKYIS LGKG FGSVELCR

hJAK3    794 YDPLGDNTGALVAVKQLQHSGPDQQRDFQREIQILKAQHSDFIVKYRGVSYGPGRQSPAL 898
rJAK3    838 YDPLGDNTGPLVAVKQLQHSGPEQQRDFQREIQILKALHCDFIVKYRGVSYGPGRQELRL 897
CONS         YDPLGDNTG LVAVKQLQHSGP+QQRDFQREIQILKA H DFIVKYRGVSYGPGRQ   L

hJAK3    899 VMEYLPSGCLRDFLQRHRG.LDASRLLLYSSQICKGMEYLGSRRCVHRDLAARNILVESE 957
rJAK3    898 VMEYLPSGCLRDFLQRHRARLHNDRLLLFAWQICKGMEYLGARRCVHRDLAARNILVESE 957
CONS         VMEYLPSGCLRDFLQRHRA L   RLLL++ QICKGMEYLG+RRCVHRDLAARNILVESE

hJAK3    958 AHVKIADFGLAKLLPLDKDYYVVREPGQSPIFWYAPESLSDNIFSRQSDVWSFGVVLYEL 1017
rJAK3    958 AHVKIADFGLAKLLPLGKDYYVVRVPGQSPIFWYAPESLSDNIFSRQSDVWSFGVVLYEL 1017
CONS         AHVKIADFGLAKLLPL KDYYVVR PGQSPIFWYAPESLSDNIFSRQSDVWSFGVVLYEL

hJAK3   1018 FTYCDKSCSPSAEFLRMMGCERDVPRLCRLLELLEEGQRLPAPPCCPAEVSCYSGWRDDI 1077
rJAK3   1018 FTYSDKSCSPSTEFLRMIGPEREGSPLCHLLELLAEGRRLPPPSTCPTEVQELMQLCWSP 1077
CONS         FTY DKSCSPS EFLRM+ GER+    LC LLELL EG+RLP P   CP EV

hJAK3   1078 CLPAE                      1082
rJAK3   1078 NPQDRPAFDTLSPQLDALWRGSPG   1101
CONS
```

FIG. 3 (PAGE 2 OF 2)

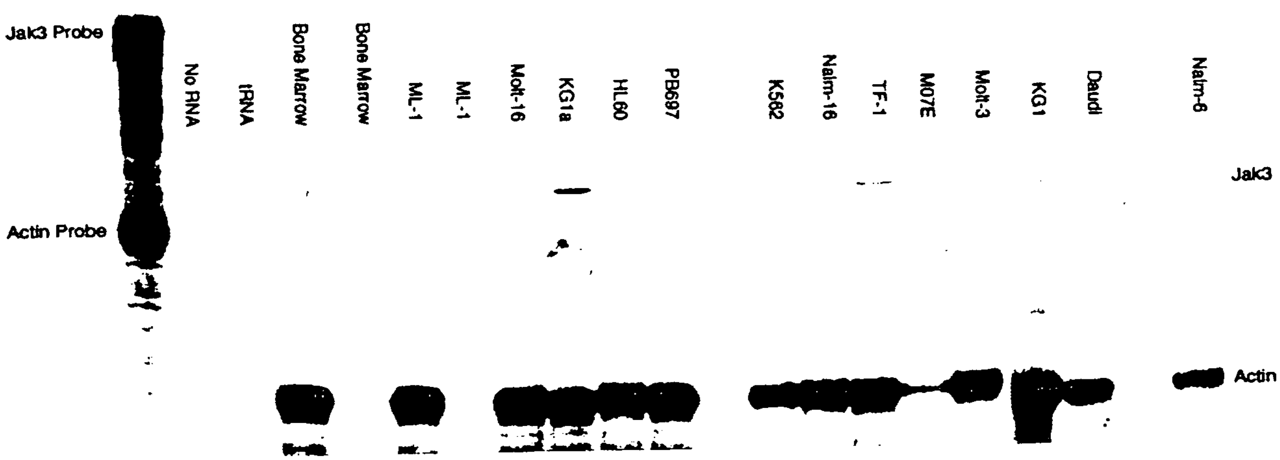

Jak3 Probe
Actin Probe
No RNA
tRNA
Bone Marrow
Bone Marrow
ML-1
ML-1
Molt-16
KG1a
HL60
PB697
K562
Nalm-16
TF-1
M07E
Molt-3
KG1
Daudi
Nalm-6
Jak3
Actin

FIG. 4a

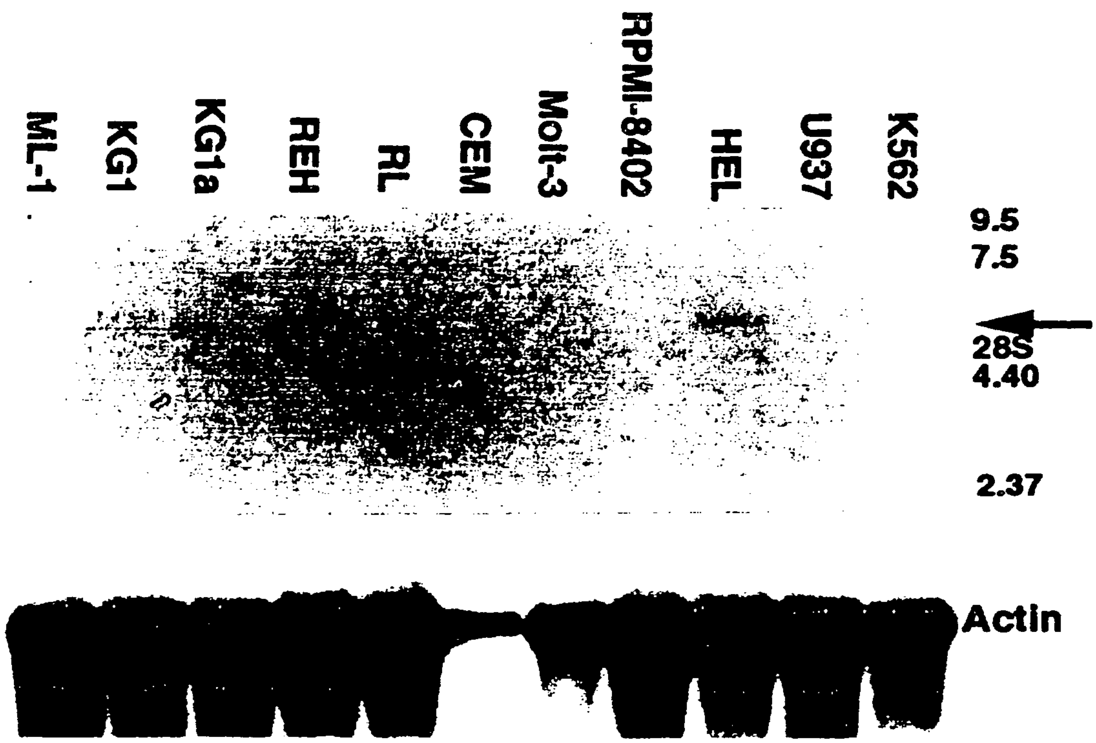

ML-1
KG1
KG1a
REH
RL
CEM
Molt-3
RPMI-8402
HEL
U937
K562
9.5
7.5
28S
4.40
2.37
Actin

FIG. 4b

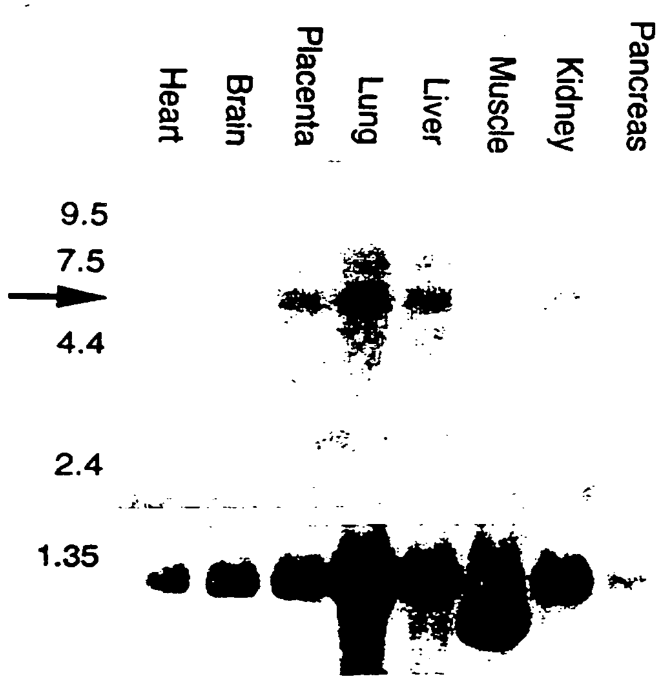

Heart
Brain
Placenta
Lung
Liver
Muscle
Kidney
Pancreas
9.5
7.5
4.4
2.4
1.35

FIG. 4c

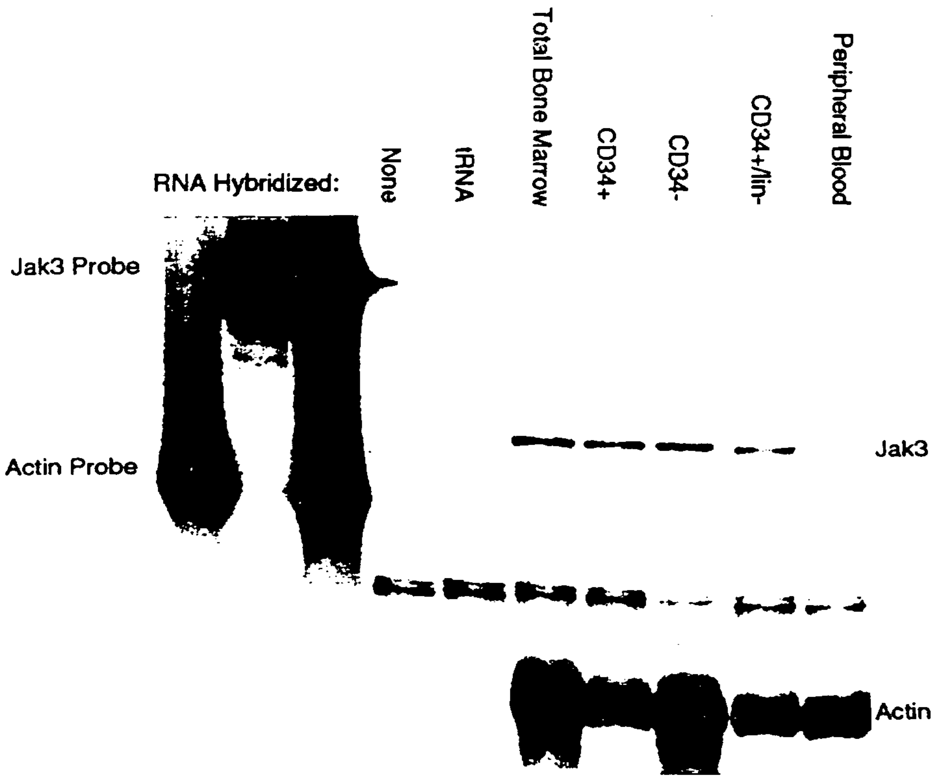


FIG. 5A

FIG. 6A

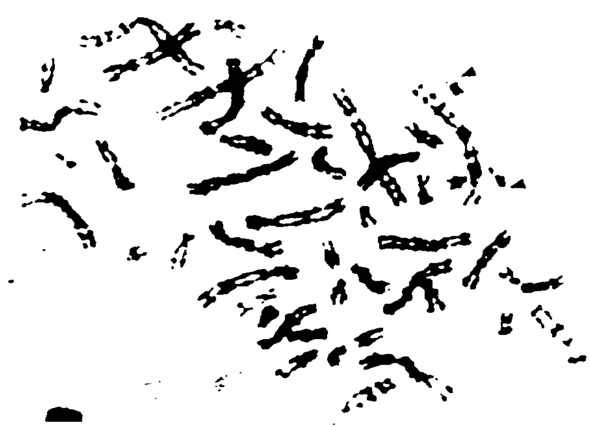
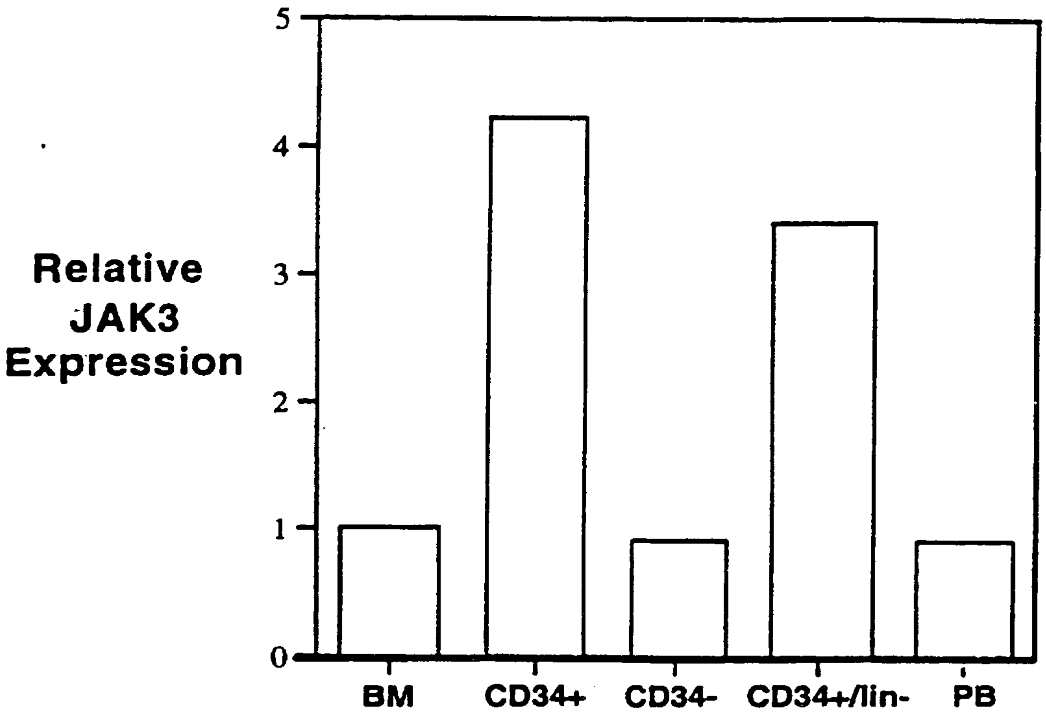
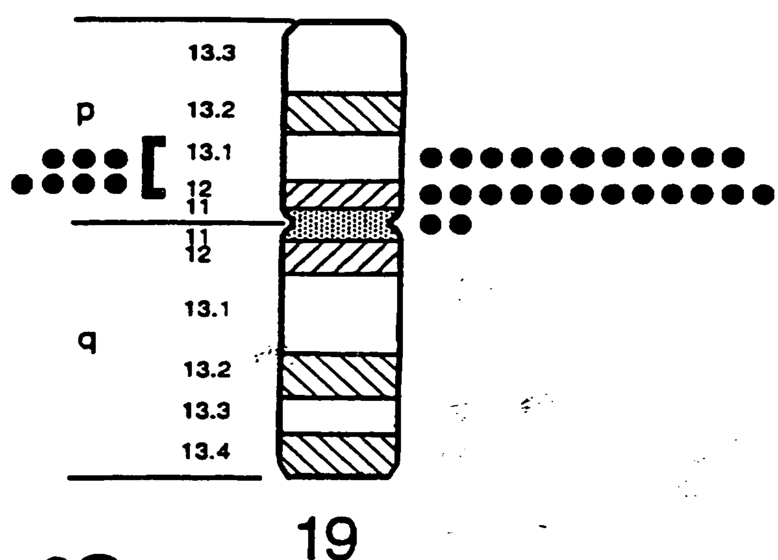


FIG. 6B



5
4
3
2
1
0
Relative
JAK3
Expression
BM
CD34+
CD34-
CD34+/lin-
PB
RNA Source:

FIG. 5B



p
q
13.3
13.2
13.1
12
11
11
12
13.1
13.2
13.3
13.4
19

FIG. 6C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/16435

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07H 21/00; C07K 14/435; C12N 15/12, 15/63, 15/74, 15/79
US CL :536/23.5; 530/350; 435/69.1, 240.2, 252.3, 254.11, 320.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.5; 530/350; 435/69.1, 240.2, 252.3, 254.11, 320.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Medline, Biosis, WPI
search terms: JAK, JAK3, cloning, DNA, tyrosine kinase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Proceedings of the National Academy of Sciences USA, Volume 91, issued July 1994, Kawamura et al, "Molecular Cloning of L-JAK, a Janus Family Protein-Tyrosine Kinase Expressed in Natural Killer Cells and Activated Leukocytes", pages 6374-6378, see pages 6375-6377.	1-6
P, Y	The Journal of Biological Chemistry, Volume 270, Number 42, issued 20 October 1995, Lai et al, "A Kinase-Deficient Splice Variant of the Human JAK3 is Expressed in Hematopoietic and Epithelial Cancer Cells", pages 25028-25036, see pages 25030-25034.	1-6

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 APRIL 1996	22 APR 1996

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Sally P. Teng
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FEBS Letters, Volume 342, issued 1994, Takahashi et al, "Molecular Cloning of Rat JAK3 , a Novel Member of the JAK Family of Protein Tyrosine Kinases", pages 124-128, see pages 126-127.	1-6
Y	Nature, Volume 370, issued 14 July 1994, Witthuhn et al, "Involvement of the Jak-3 Janus Kinase in Signalling by Interleukins 2 and 4 in Lymphoid and Myeloid Cells", see pages 153-157, see entire document.	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/16435

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-6, drawn to JAK3 polypeptide and its encoding DNA.
Group II, claims 7-9, drawn to antibodies specific for JAK3.
Group III, claims 10-14, 16, 17, 21-24, 36, 39, and 40, drawn to a method of detection using nucleic acid as the probe.
Group IV, claims 10, 15, 16, 18-24, and 36-38, drawn to a method of detection using antibodies as the probe.
Group V, claims 25-35, drawn to an in vivo method of treatment.
Group VI, claims 41 and 42, drawn to a method of stimulating hematopoietic cell proliferation.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
Claims 10, 16, 21-24, 36, and 37 are in two separate groups, Groups III and IV, because the method of Group III uses a nucleic acid probe where the method of Group IV uses an antibody probe. The nucleic acid probe of III has a different structure and functions by a different targetting mechanism from the antibody probe of IV. Since these special technical features are not the same or corresponding, Groups III and IV are not linked by a special technical feature. The special technical feature of Group I is a JAK3 polypeptide having a specific amino acid sequence and its encoding polynucleotide, while the special technical feature of Group II is an antibody that binds to JAK3 but does not have the amino acid sequence of JAK3. The special technical features of Groups I and II are not the same because the polypeptide and polynucleotide of Group I are structurally and functionally different from the antibody of Group II. Groups III, V, and VI are directed to distinct methods of using nucleic acids and Group IV is directed to a method of using antibodies. Group I and Groups III, V, and VI do not share a special technical feature because the methods of Group III, V, and VI do not require the polynucleotide of Group I. Further, each of the methods in Groups III, V, and VI is performed with a specific nucleic acid. The methods of Groups III, V, and VI do not require the antibodies of Group IV. Groups II and IV do not share a special technical feature because the method of Group IV does not require the antibodies of Group II. The method of Group IV does not require the product of Group I.The Groups are not linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.